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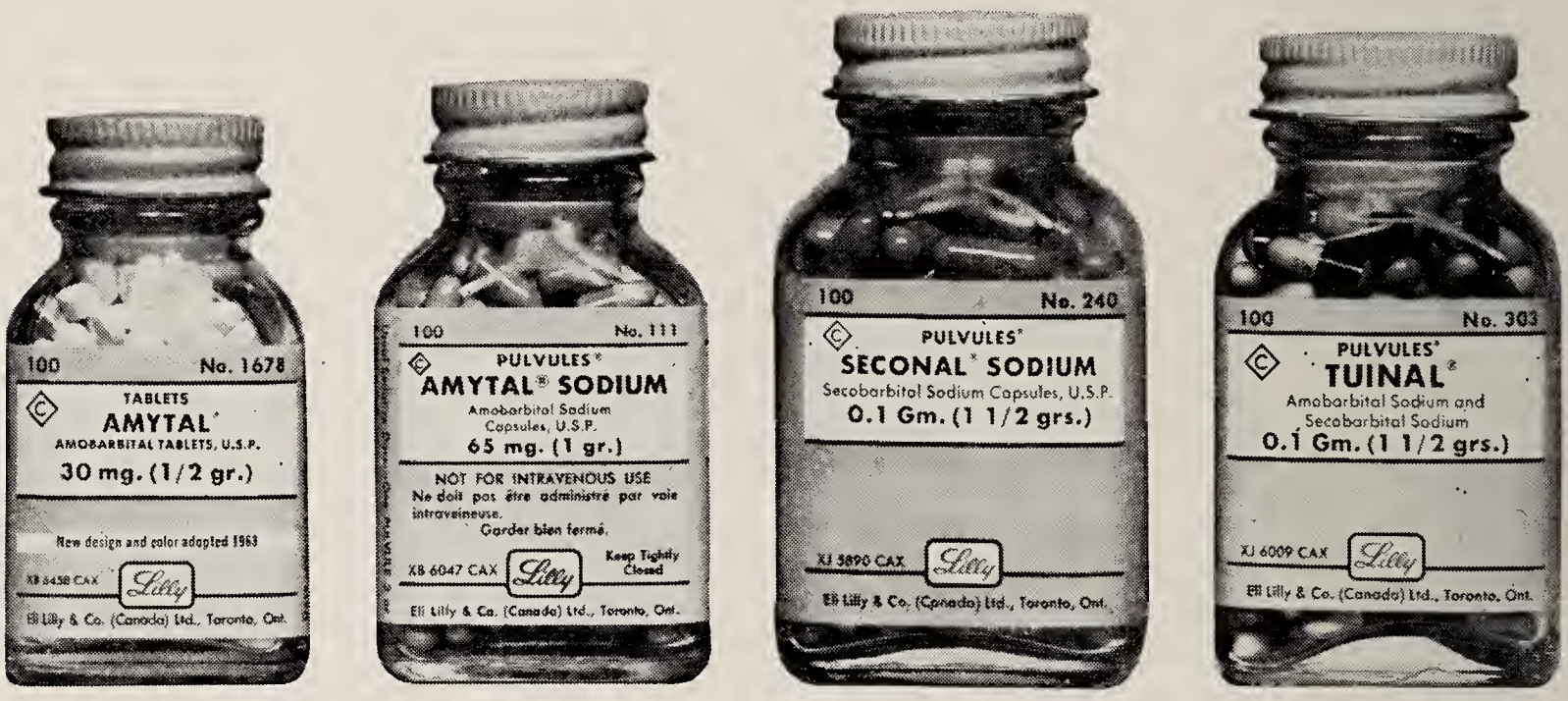

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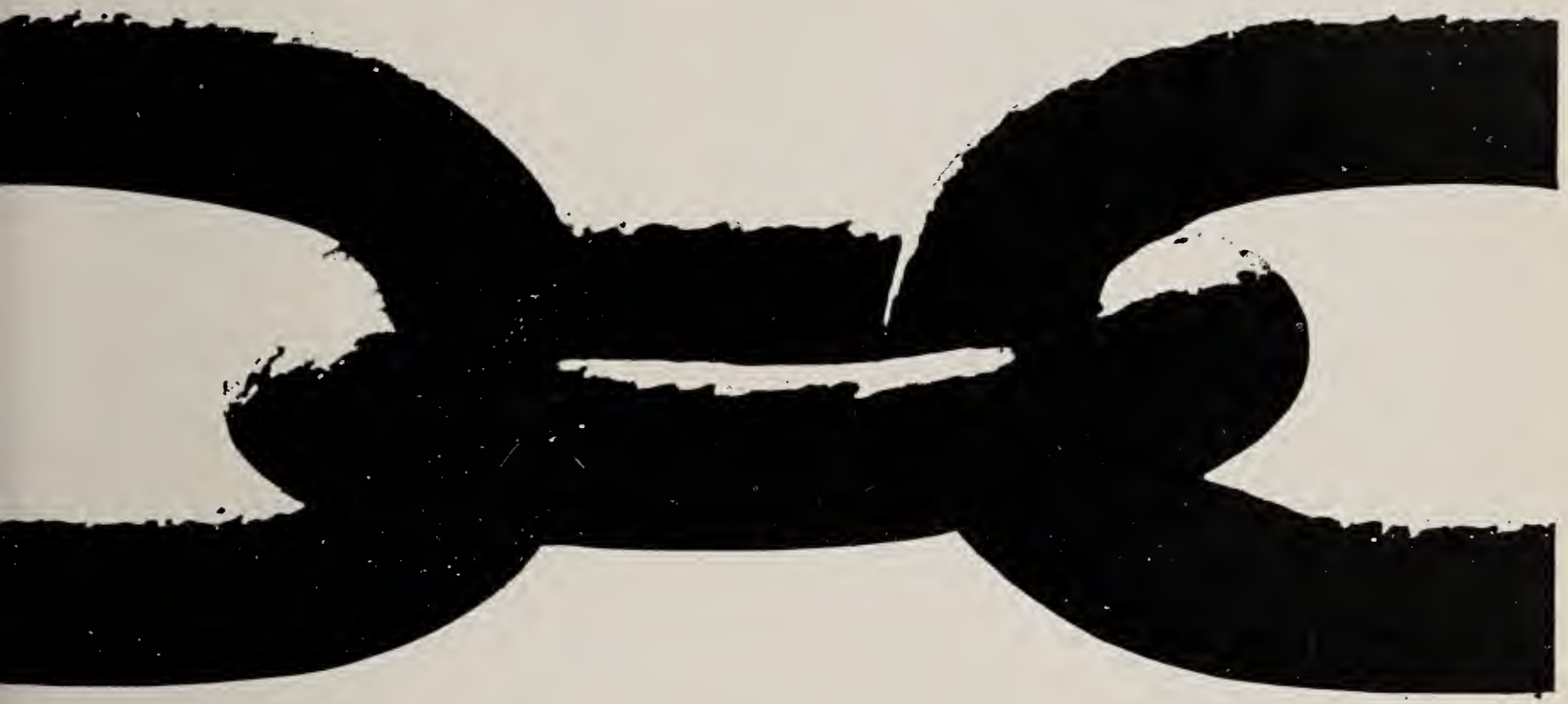

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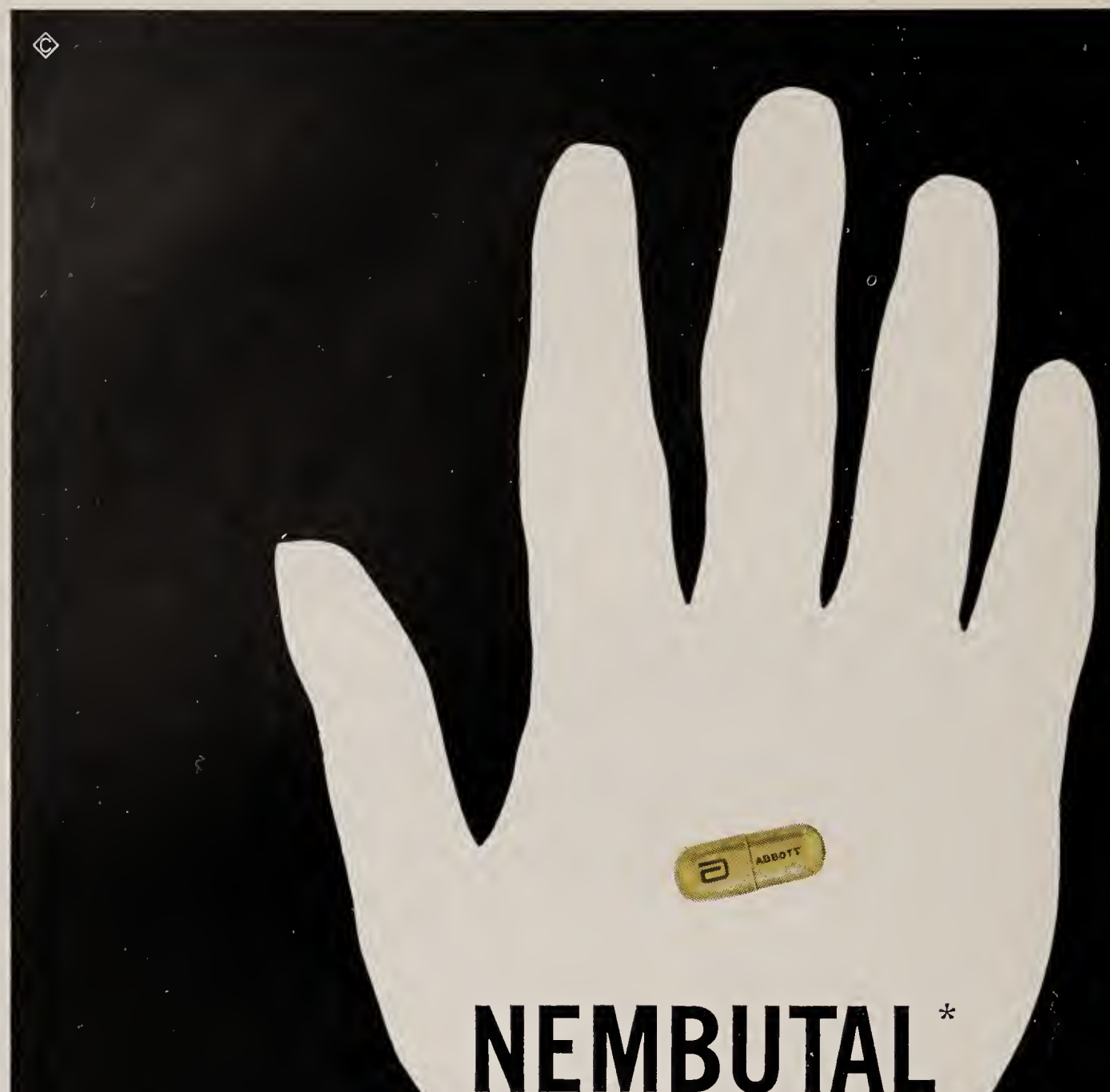

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Editorial

Obesity is a clinical problem of high incidence, and is a common denominator in a wide range of disorders foremost among which are diabetes mellitus, atherosclerosis, hypertension and biliary tract disease. There is currently a great deal of interest in the biochemical, metabolic and physiologic aspects of the condition. Studies in these areas are shedding light on normal homeostatic mechanisms, on altered mechanisms in the obese and fasting states, and on the derangements common to the other conditions to which the obese patient seems predisposed. Because investigation of the condition involves study of the most fundamental aspects of energy metabolism and overlaps research in other important areas, it was considered in putting together an issue on Fat Metabolism that the clinical problem of obesity merited the major consideration given to it here.

The first article deals with the metabolic alterations present in the obese and fasting states. Abnormal patterns of carbohydrate and fat metabolism are characteristic of the obese state and may be responsible for the genesis as well as the perpetuation of the condition. In addition, the obese patient shows an abnormal response to starvation. Since partial starvation is the fundamental tool in present day therapy of the overweight patient, understanding of the physiology of weight reduction and its derangement in the obese patient is necessary for rational application of therapy.

Recent Advances is concerned with a topic of equally fundamental importance in the genesis and maintenance of obesity. Hunger homeostasis is a remarkable mechanism in the weight stable individual. Weight stability is absolutely dependent on the equality of average intake to average energy expenditure; a yearly variation of weight of two pounds reflects an average daily deviation from balance by a mere twenty Calories. Thus a very accurate day to day regulation of intake appears to be operating.

It is becoming clear that the site of regulation of hunger and therefore of food intake is located within the hypothalamus. A satiety centre in this region appears to operate by inhibiting hunger after its receptors cells have taken up a certain quantity of glucose. The rate of this uptake depends on the amount of available circulating glucose. The amount of circulating glucose in turn is dependent on the nutritional status of the peripheral tissues; decreased tissue demands for glucose result in more available circulating glucose, more glucose is taken up in the satiety centre, and hunger is inhibited. In this way hunger is related to nutritional status.

It is interesting to speculate how this mechanism of hunger regulation might be affected by the known alterations of tissue metabolism in the obese state. Studies of starvation in obese patients demonstrate a deficient capacity for lipolysis. These patients under normal conditions also have increased plasma levels of insulin, which is known to enhance lipogenesis and to promote peripheral uptake of glucose. Deficient lipolysis, enhanced lipogenesis and increased glucose uptake would appear to combine to make adipose tissue a preferred site of glucose uptake, at the expense of the other tissues including the hypothalamic glucoreceptors, with the result that the hypothalamic mechanisms fail to reflect the overfed state of the adipose tissues.

Weight stability in the overweight patient is attained when the rate of lipolysis rises to meet the rate of lipogenesis. Possibly as a consequence of a deficient lipolytic capacity, this balance is not achieved until the attainment of an abnormally large adipose mass. Once equilibrium is achieved the large uptake of glucose by the adipose tissues would be compensated by an equivalent output of free fatty acids and glycerol. The use of these as energy substrates by the peripheral tissues would decrease their requirement for glucose. Circulating glucose would then be available for hypothalamic uptake in adequate amounts to suppress hunger to the degree necessary for weight stability.

On the other hand, altered hypothalamic regulation might be a primary phenomenon in obesity with the metabolic derangements being secondary. Obesity may represent an altered "set" of the glucoreceptive mechanism so that glucoreceptors are less sensitive to available circulating glucose.

In any case it is important to understand that the normal individual's weight control comes not from a conscious and rational regulation of caloric intake, but rather from a normal response to a degree of hunger which accurately reflects his nutritional state. In the overweight patient one may be dealing with a *normal* response to an *abnormal* degree of hunger which does not accurately reflect his nutritional status. If correct, this would mean that in training the overweight patients to eat less one is training him to respond to a lesser degree than normal to hunger stimuli — and this may be an inadequate and unrealistic approach.

EDITORIAL

The article on medical management of the obese patient presents a comprehensive approach to the notoriously difficult problem of achieving lasting weight reduction. The need for *permanent* alteration of eating habit is stressed. Overweight is a serious health problem to which the physician should be constantly alert in his patients. It should be approached thoughtfully and energetically.

The clinical coincidence of obesity, hypertension and diabetes is a striking one and has many fascinating implications. The high incidence of overweight in mature onset diabetes may be a consequence of the high levels of circulating insulin found in this disorder. Most tissues appear to be relatively resistant to the circulating insulin in mature onset diabetes, but adipose tissue retains its sensitivity. Lipogenesis is favoured while other tissues, presumably including the hypothalamic glucoreceptors, may be relatively glucose deprived. Here is another situation where degree of hunger may fail to reflect the overfed state of the adipose stores.

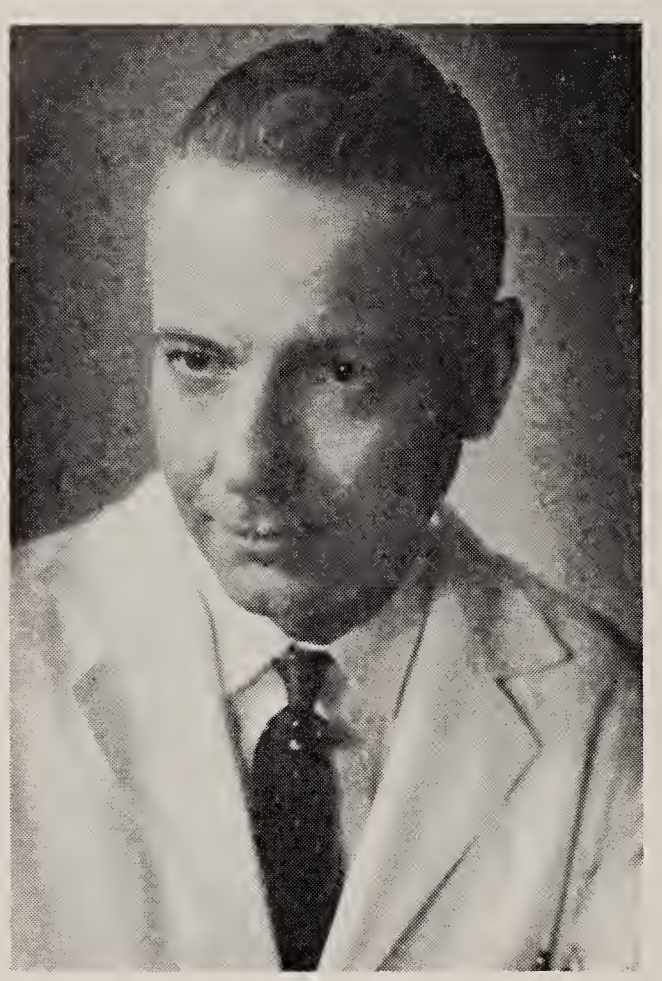
Some recent and highly provocative findings are presented in the discussion of the immunological aspects of diabetes mellitus. The etiology and pathogenesis of diabetes remains a mystery today over forty years after the discovery of insulin. It has been apparent for some time that in the maturity onset diabetic plasma insulin levels are elevated beyond the normal, and for this reason some form of insulin antagonism has long been considered a possible factor in the pathogenesis of the disorder. Totally without accepted explanation is the microangiopathy which underlies so much of the morbidity and mortality associated with diabetes. Evidence is now appearing to suggest a possible immunological basis for both the insulin hyporesponsiveness and the microangiopathy. The duplication of diabetes in experimental animals by deliberately evoking immune responses to insulin demonstrates that an immunological basis is at least possible in the pathogenesis of human diabetes. Nevertheless scientific conservatism is in order and only time and much research effort will reveal what is significant, what is misinterpretation and what is artifact in this new chapter in one of the most fascinating of metabolic disorders.

While work in the fields of biochemistry and physiology has demonstrated genuine metabolic derangements in obesity, it has by no means been established that these are primary in the genesis of obesity, and psychological mechanisms may well play a significant role. It is important to realize that, regardless of the role of these factors, it is the patient's psychological make-up, interacting with that of his physician, that ultimately determines the outcome of attempted weight reduction.

The guest editorial for this issue has been written by Dr. W. Stanley Hartroft. Dr. Hartroft has made a tremendous contribution toward the understanding of the role of dietary lipotropic factors in hepatic, cardiovascular and renal pathology. His contribution to the literature has been a prolific one, and in testimony to his standing is his participation in a great number of professional publications, societies and conferences in North and South America and abroad. We are honoured to have him participate in this issue.

NORMAN ISCOVE

Guest Editorial



W. STANLEY HARTROFT
B.Sc.(Med.), M.D., Ph.D., LL.D.(Hon.)
Director, Research Institute of The Hospital for Sick Children, and Professor of Physiology, University of Toronto.

Dr. Hartroft was born in Calgary, Alberta, and received his M.D. from the University of Alberta. The latter part of the last War was spent as a resident in Pathology at the Toronto General Hospital and later as Major-Pathologist with the Canadian Army abroad. On his return to Toronto as a Research Associate in the Banting and Best Department of Medical Research he became interested in the pathological effects of dietary choline deficiency. The years 1953 to 1961 were spent in the U.S.A. as Professor and Chairman of the Department of Pathology in the Washington University School of Medicine. In 1961 he accepted his current post as Director of The Research Institute at Toronto's Hospital for Sick Children and in the same year was named Professor in the Department of Physiology. The influence of dietary lipiotropic factors on hepatic, cardiovascular and renal pathology has remained his dominant interest. His work has demonstrated the significance of lipotropic factor deficiency in the pathogenesis of hepatic cirrhosis. He has investigated and demonstrated the influences of cholesterol intake and metabolism, quality of dietary fat, and plasma lipid levels on atherosclerosis and intravascular thrombosis. In recent years he has used the electron microscope to investigate the fine structural cellular changes induced by dietary insult.

Fats, Diet And Disease

During the past decade, advances in our understanding of the importance of dietary fats in both health and disease have been matched only by the increase in knowledge concerning their absorption, transport and metabolism. Technical advances, most notably thin-layer and gas-liquid chromatography, have been, to a considerable extent, responsible for this near-revolution; before their advent only a dozen years ago, one of my preceptors advised his graduate students to choose almost any other field of investigation other than that related to lipids, because as he pointed out, the methodologies (then) were quite inadequate. Beginning with establishment of the need for essential fatty acids in human nutrition, the probable importance of polyunsaturated dietary fats, and knowledge today of pathways of intermediate metabolism involving the synthesis and breakdown of lipids, such advice would now never be offered. On the contrary, the field of fat metabolism in its broadest sense is not only a rapidly expanding one, but also one which offers the young investigator tremendous scope for the exercise of his originality both as a basic scientist and as a clinical investigator.

But a great many fundamental questions are still unanswered. One of the simplest, yet most important of them: what are the optimal amounts and kinds of dietary fats which will permit normal human growth and development during the paediatric period and what is the optimum to favour continued health in adult life? The need for at least small amounts of the essential fatty acids in newborn infants was clearly demonstrated by the late Hansen of Texas and California but beyond this point, one paediatrician's opinion is as good as another's. To protect their cardiovascular systems, adults are being urged nowadays to reduce by half the 45-50% of total calories now supplied by fat in their diet and to double or even treble the proportion of polyunsaturated fats in this reduced amount. Because it is difficult to increase

the calories supplied by protein (without also elevating the fat content) much above the level now present in the well-fed Canadian's diet, the reduction in fat must mean a perhaps significant increase in dietary carbohydrate. Even if such a change in established dietary patterns should be safe for the adult, will it permit ideal growth and maturation of infants? The answers to these and more fundamental questions which will provide the basis for the clinical solutions can only come from the continued efforts of the lipid biochemist, the physiologist and the basic nutritionist using multidisciplinary approaches.

Even the scientist who rarely picks up the fashion magazines of his wife, is aware that the popular cosmetic, as well as health, fad at present would have us all nourished not much more than the Belsen victims of 20 years ago. Here again, available data do not tell us from a health point (aside from the coutouriers' view) that should be the ideal amount of fat to be stored in physiologic adipose tissue depots. Teleologically, in the past generous fat stores must have helped man weather periods of starvation and illness when food could either not be eaten or not be absorbed. If modern technology and medicine have minimized the risk that the individual might someday have to live off his own tissues, does this fact mean that the fashion designers are right also from a health point?

Stark leanness was not always the ideal of beauty and in other cultures and other days obesity, even to the point of grossness, was admired. It is obvious that the only answer at present that makes sense is moderation in dietary practices related not only to total caloric intake but also to the amount and kind of fat we consume daily. Some of those devoted only to study of one major disease, such as atheromata and myocardial infarction, might have us go further, but fat has more rôles to play than merely to build up atheromatous plaques.

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Metabolic Patterns In The Obese And Reducing Patient

A. Weinstein 6T7

In recent years much of the normal metabolism of adipose tissue has been elucidated. In addition there has been an increasing amount of interest in the state of carbohydrate and fat metabolism in the obese state. It has become clear that there are metabolic abnormalities associated with obesity which are relevant perhaps to the establishment and certainly to the maintenance of the obese condition. The mechanisms of weight reduction under conditions of starvation are also significantly altered in the obese patient. Before considering these abnormalities, the important features of normal adipose tissue metabolism will be reviewed.

NORMAL FAT METABOLISM

LIPOGENESIS

Fat synthesized in adipose tissue is derived from a number of precursors (Fig. 1). Glycerol in the form of alpha-glycerophosphate is utilized from the glycolytic pathway within the fat cell. Most of the fatty acid used is synthesized in the liver from acetyl CoA and CO_2 — products of the glycolytic and redox pathways. This synthesis is dependent on the presence of NADPH (TPNH) generated by the metabolism of glucose via the pentose phosphate (hexose monophosphate) shunt. Esterification of the glycerophosphate and fatty acids is accomplished within the fat cell and is dependent on a continuous supply of ATP.

It is evident that fat synthesis is inseparably linked with carbohydrate metabolism. Because fat synthesis depends on functioning glycolytic and pentose phosphate pathways, the availability of glucose and insulin is an absolute prerequisite for it to occur.

Some of the precursors for fat synthesis are obtained by assimilation of circulating triglyceride. Plasma triglycerides are mainly in the form of lipoproteins. These can be hydrolysed in fat cells by the enzyme lipoprotein lipase. During uptake, the triglycerides so released are further hydrolysed to fatty acids and glycerol. The fatty acids may be utilized in fat synthesis but the glycerol cannot be reesterified in the non-phosphated form and is released into the circulation.

PLASMA FREE FATTY ACIDS AND FAT MOBILIZATION

Most of the plasma free fatty acids (FFA) are derived from triglyceride breakdown in adipose tissue. A small amount is contributed in the form of chylomicra by intestinal absorption following a fatty meal. Free fatty acids are taken up by tissue cells where they serve as a source of energy and, in the case of liver and adipose tissue, also as a substrate for triglyceride formation. The plasma fatty acid level represents the point of equilibrium between the rates of fatty acid release and tissue uptake. Normal early morning plasma values are around 450-500 microequivalents per litre.

The important influences on plasma fatty acid levels are hormonal and dietary. Epinephrine and growth hormone are lipolytic and thus tend to raise free fatty acid levels. In fasting, carbohydrate stores are depleted and become unavailable to tissues for either triglyceride synthesis or energy production. Lipolysis then predominates over lipogenesis, plasma free fatty acid levels increase, and free fatty acids become the main substrate for oxidation in peripheral tissues (with the exception of nerve cells and red blood cells). Liver cells take up large amounts of the free fatty acids which are then metabolized to acetyl CoA, ketone bodies and triglycerides, with resulting fatty liver and ketosis. The phenomenon is referred to as *fat mobilization.*

METABOLIC ALTERATIONS IN OBESITY AND STARVATION

In a discussion of obesity there are two main types which should be distinguished: those in which there has been a recent loss or gain in weight (dynamic obesity) and those which have shown little fluctuation for some time (stable obesity). It is the latter condition which demonstrates most of the biochemical abnormalities to be discussed and which is often very resistant to treatment, even extreme fasting.

PLASMA FREE FATTY ACIDS

Plasma free fatty acid levels are increased in obesity, reflecting a constantly elevated lipolytic rate. This may be due entirely to the increased adipose tissue mass rather than to an elevated rate of lipolysis per fat cell. Fat becomes the body's main fuel source with a reduction of the respiratory quotient to about 0.7. Fasting and refeeding produce less of a change in free fatty acid levels than in the non-obese subject, and there is a diminished capability for fat mobilization.

CARBOHYDRATE METABOLISM

In the obese patient there appears to be a relative tissue insensitivity to insulin. Plasma insulin levels are higher than normal and there is an exaggerated insulin response to a glucose load. Nevertheless, although fasting bloor sugars are normal, tissue uptake of an added glucose load is deficient and a diabetic type of glucose tolerance curve is obtained.

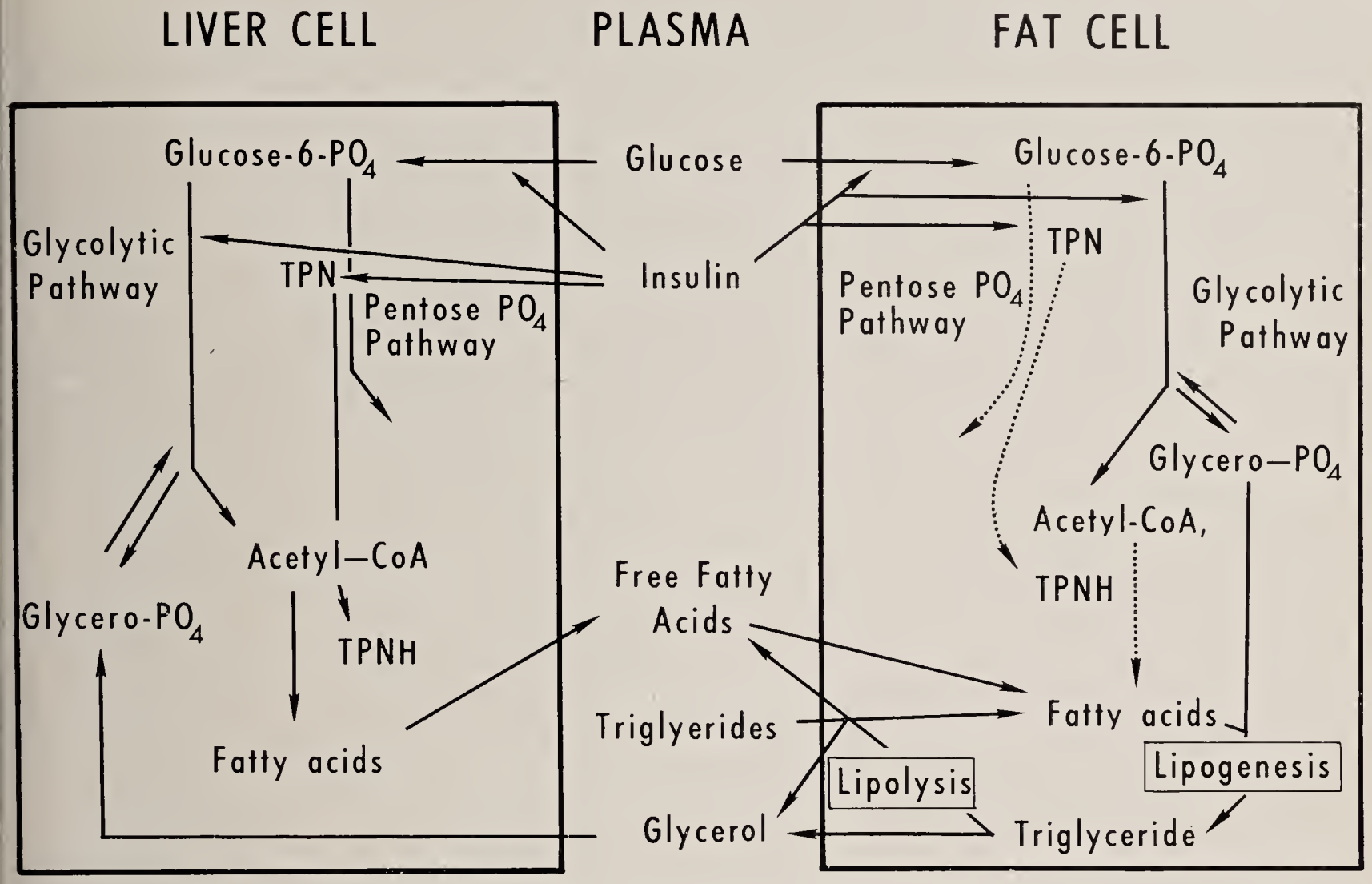

FIG. 1: The pathways of lipogenesis and lipolysis are illustrated. Fat synthesis is dependent on precursors and coenzymes supplied by carbohydrate metabolism. There is a close interdependence between adipose tissue and the liver.

It has been suggested that elevated levels of free fatty acids may be responsible for a relative insulin insensitivity by directly inhibiting glucose uptake or its oxidation. This inhibition may not affect adipose tissue so that glucose loads would be diverted into lipogenesis, perpetuating the obese state.

HORMONES

Levels of growth hormone are normal in the obese state but with fasting there is a diminished rise of growth hormone titre compared to that seen in fasting normal subjects.

There is a decreased lipolytic response to epinephrine.

A generalized hypometabolic state exists in the obese patient, with a low level of oxidation of all energy substrates. Thyroid function is usually normal; however, in some instances exogenous thyroid hormone will increase metabolism and will restore the ability of epinephrine to induce lipolysis.

FLUIDS AND ELECTOLYTES

There is a marked tendency to accumulate salt and water and a decreased ability to excrete a salt and water load. Underlying factors are a diminished renal blood flow and glomerular filtration rate, and an elevated level of antidiuretic hormone. Since the oxidation of 100 grams of fatty acid yields over 110 grams of "metabolic" water which must be excreted before weight loss can occur, it is clear that these alterations help to explain the inability of some obese patients to lose weight in spite of severe dietary restriction.

INFLUENCE OF EATING PATTERN

The importance of eating pattern has been demonstrated experimentally. Two groups of rats were placed on isocaloric diets. One group was given one large meal per day while the other group was given small feedings throughout the day: both groups had an identical total caloric intake. There was no significant difference in weight gain between the two groups; however, the former showed increased lipogenesis and fat storage while the latter group stored more of the weight as muscle protein. It is suggested that large carbohydrate loads delivered over a short time stimulate increased metabolism of carbohydrates via the pentose phosphate pathway. In this way increased amounts of NADPH are made available, stimulating lipogenesis. However, it is presently felt that in humans the major mode of activation of this pathway is by means of decreased levels of NADPH under conditions of increased fat synthesis, i.e. the relationship of the pathway to lipogenesis is a passive rather than an active one.

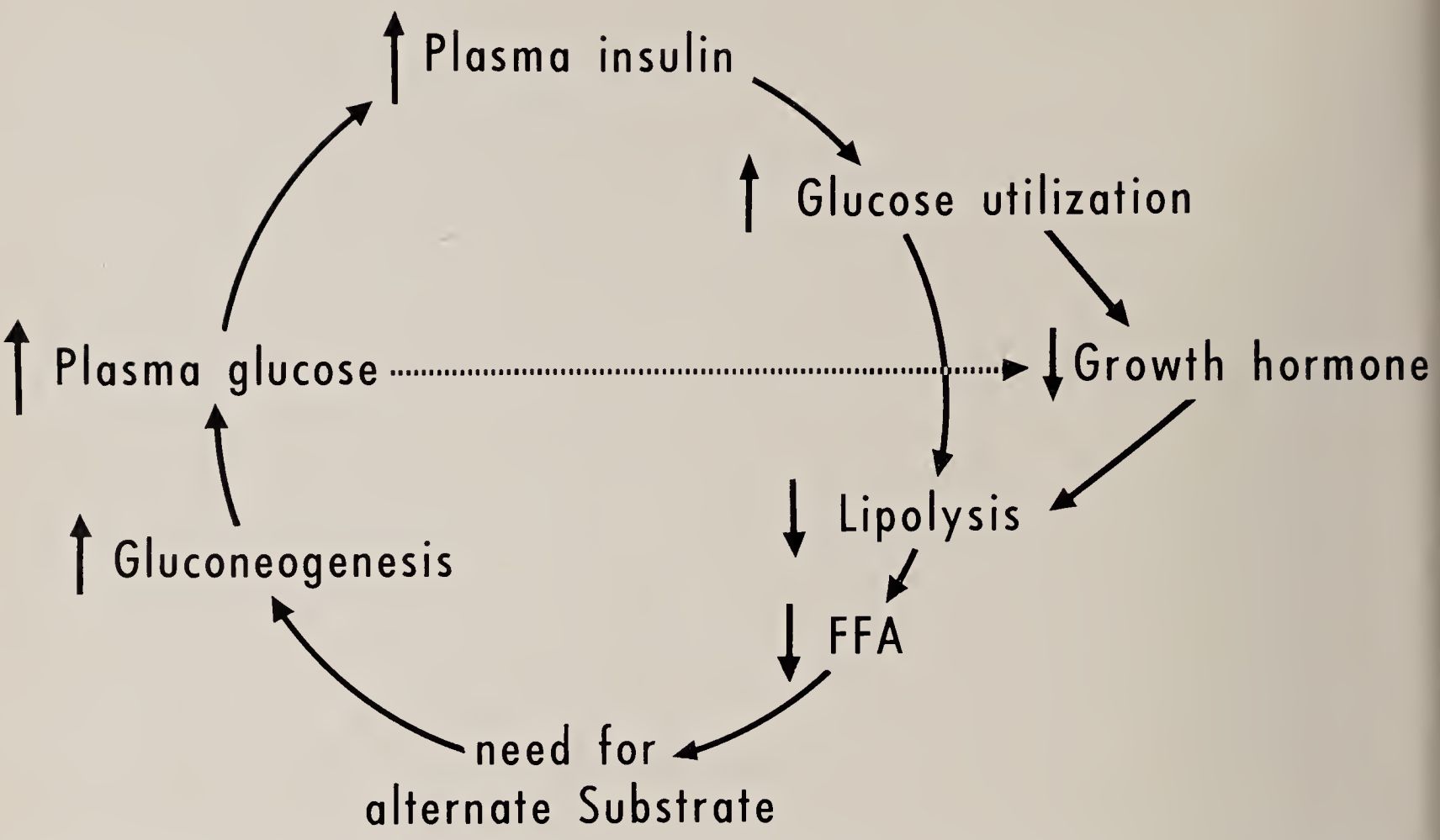

FIG. 2: A vicious cycle in the fasting obese patient is illustrated in which elevated insulin levels inhibit lipolysis, leading to prolonged gluconeogenesis which supports the elevated insulin.

EFFECTS OF PROLONGED FASTING

Under conditions of prolonged fasting obese patients show:

1. subnormal rate of increase of plasma free fatty acids
2. resistance to ketosis
3. smaller increase in plasma growth hormone
4. diminished response to lipolytic agents such as epinephrine and growth hormone
5. increased glucose uptake by muscle
6. abnormally high plasma insulin
7. abnormally high proportion of weight loss derived from lean body mass (67%) rather than from adipose tissue.

During prolonged severe caloric restriction in normal subjects carbohydrate and protein are initially relied upon for energy production, but after a few days there is a switch to predominantly fat metabolism, accompanied by a rising plasma free fatty acid level. In obese patients a prolonged reliance on carbohydrate and protein with a delay in the transition to fat breakdown has been demonstrated. Carbohydrate stores are soon depleted, leaving body protein as the major source of utilizable energy. Gluconeogenesis increases although the mechanism of the stimulus evoking the elevation is not clear. The blood glucose provided by gluconeogenesis supports the elevated insulin level. The elevated insulin in turn contributes to the inhibition of lipolysis, and a self-perpetuating cycle is established (Fig. 2). The role of growth hormone in this sequence is not understood.

In summary, the obese state is characterized by greatly enhanced lipogenesis and diminished lipolysis even during starvation. The metabolic alterations involved may be inherited, may be adaptive to many years of poor and excessive eating habits, or may be both. Hopefully, understanding of the metabolic derangements and of their etiology will lead to more effective treatment of the condition.

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Recent Advances

The Hypothalamus And Obesity

As recently as 12 years ago the only accepted etiology of obesity was gluttony. The compulsive input of food was greater than its utilization and the difference was turned into depot fat and stored. Since 1953 the problem of obesity has come under intensive review and much experimental work has been done to try to demonstrate the basic mechanisms involved in the etiology. Many factors have been implicated and undoubtedly a complex host of interrelationships exists. Some of these factors include endocrine, psychosomatic, environmental, genetic, and physiologic disturbances.[1]

The first understanding of sensory aspects of hunger and satiety came with the work of Jean Mayer. He proposed a glucostatic mechanism of control in the ventromedial area of the hypothalamus. Earlier experimental work showed that bilateral destruction of the ventromedial nuclei caused hyperphagia and subsequent obesity.[2] According to Mayer's work, the regulation of feeding behaviour resided in the ability of some cellular components of the ventromedial area of the hypothalamus to recognize the levels of extracellular or intracellular glucose. Redding, Bowers, and Schally observed, however, that hyperglycemia, artificially produced in a number of different ways, did not always result in a loss of appetite.[3] Indeed, in diabetes mellitus obesity is often present despite increased blood glucose levels.

It is accepted that there is a hunger (feeding) centre and a satiety centre in the hypothalamus. The mechanisms by which they operate is not known with certainty but the work of Edelman *et al* provides a working hypothesis.[4] This group postulates a continually active feeding centre in the lateral part of the hypothalamus which induces a sustained urge to eat, and a relatively quiescent ventromedial satiety centre which, when activated, suppresses the urge. The satiety centre responds to glucose at specific glucoreceptor sites in or on the cells in this area. The active cell is the glial cell. It has a greater intrinsic rate of metabolism of glucose and in addition may be more richly supplied with arterial blood, enhancing the quantity of glucose available, and hence there is preferential uptake of glucose. Metabolism of a specific quantity of glucose in a glial cell results in the generation of an action potential on a satiety neuron. The more satiety neurons activated, the greater the suppression of the hunger centre. This mechanism was studied by means of gold thioglucose. When ingested into the cell, the glucose is metabolized and if enough thioglucose is present, the gold which is left over is toxic to the cell and causes necrosis. With the destruction of enough cells, the associated nerve is destroyed and this removes its inhibiting effect on the hunger centre, resulting in hyperphagia and obesity. This hypothesis was supported by the finding that hyperglycemia gave rise to increased electrical activity of the satiety centre and decreased activity in the hunger centre. Hypoglycemia had an opposite effect. There were no effects in either state on the cortex and similar changes were not produced by proteins or fat.[5]

Other factors involving the hypothalamus besides glucose levels undoubtedly are operating. The anterior pituitary may play an important role. A new anterior pituitary hormone, lipotropin, was discovered by Li in 1964.[6] At that time it was noted that glucose uptake decreased in the epididymal fat pad of hypophysectomized rats. The hypothalamus was implicated in this scheme because control of anterior pituitary hormones can be effected via peptide-like materials formed in the hypothalamus and secreted into the hypophyseal portal system. Such a substance has not yet been found controlling lipotropin. Other factors would include the quantity of liver glycogen and the mechanisms for glycogen synthesis, levels of non-esterified fatty acids, and the status of the fat depots; these are also monitored to some extent by the hypothalamus via its control of anterior pituitary secretions. There is a direct pathway between the limbic lobe and the hypothalamus.[7] Although the exact function of the limbic lobe is not known it has been associated in governing conditioning, habits, volition, recognition, awareness, and discrimination. These factors can affect obesity and this implies another hypothalamic mechanism. The exact role of each of these parameters remains to be seen but at this point they show that the underlying mechanisms of obesity are extremely complex and will continue to be the subject for intensive research in the future.

W. Cass 6T8

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The Physician's Role In Weight Control

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Obesity is a sign of many problems, reflecting disturbances of physiological, biochemical, psychological and social function. There is much that is yet unknown about the underlying mechanisms of fat accumulation and much that is controversial about the management of the individual patient. In this discussion, emphasis will be on certain practical aspects of the problem—incidence, onset, prevention and therapy.

I Incidence, Onset and Contributing Factors

It has been estimated that 20% of all persons over 30 are 10% *overweight,* another 10% are 15% overweight or *obese,,* an additional 3% are over 20% overweight and *seriously obese.* In total then, 1 out of every 3 adults is 10% or more above his ideal weight.

The stages in the human life cycle when weight gain is the most likely are infancy, the onset of puberty; for women, the early twenties, pregnancy and the menopause; for men, the period between 25 and 40 with an accelerated gain at 40 and after. The result of execessive accumulation of fat by the time of puberty is the so-called juvenile obesity; this type usually continues as severe adult obesity. Among the contributing factors in this early-onset obesity are lack of physical exercise, environmental factors such as a great stress on food and parental anxiety about nutrition and eating habits, psychologic responses in which food is sought in times of worry and stress, and metabolic alterations both congenital and acquired. It is interesting that the parents of most of these youngsters are also obese. Overweight commencing in adulthood is of two types—the so-called maturity-onset or *thermodynamic obesity* based strictly on caloric imbalance without significant associated mental or emotional problems, and secondly the group with *hyperphagia of psychiatric origin.*

In the majority of overweight adults the main factor is an insidious caloric imbalance — more energy consumed than expended. It is insidious because it takes so few extra Calories—a surplus of 10 per day or 3650 per year—to realize an annual weight gain of one pound. At this rate—10 pounds per decade—it's easy to be 30 pounds heavier at 55 than at 25. Age itself is a factor, and weight gain occurs even if food intake and exercise continue at constant levels, since basal metabolic rate gradually decreases with advancing years—a three percent reduction by age 35, nine percent by age 55 and 17 percent after 65 years.

II Prevention

The preventive approach is often neglected. Ideally weight control should be discussed with every new patient seen by general practitioners and many of the specialists, but particularly with those persons presenting with medical problems where obesity would prejudice the overall prognosis. The physician has a number of excellent opportunities for the promotion of weight control. Two of these are presented by the pregnant woman and by the mother of young children. At both times, most women are receptive to advice. Weight gain in pregnancy should be limited to 20 to 25 pounds; this is an appropriate time for the whole family to become more calorie conscious. Parents should be advised as to what constitutes a healthy and well-developed child; it should be made quite clear that an overweight baby is not necessarily a healthy baby. And finally prevention may frequently be promoted through community efforts such as talks to service clubs, professional organizations and to high school students.

Both prevention and therapy must take cognizance of why weight should be controlled. Cosmetic reasons should not be underestimated—indeed they are apt to compel more persons to watch calories than any which the physician can advance. The undesirability of obesity becomes apparent when one considers the associated complications and reduction in life expectancy. It can be estimated that being 25 pounds overweight reduces the age to which a person can expect to live by 25 percent. Mortality rates rise by 22 to 74 percent with weights five to 25 percent or more above ideal. The commonest complications of obesity are diabetes mellitus, hypertension and arteriosclerosis, cholelithiasis, coronary insufficiency, gout, degenerative arthritis, toxemia of pregnancy, varicose veins, hernia, respiratory difficulties, intertrigo, the mental and emotional stress created by obesity itself, and a proneness to accidents.

III Evaluation of a Patient

The evaluation of any patient's weight must never be undertaken arbitrarily. Height and weight tables must be interpreted for each person, in terms of his own somatotype; a physician's experience and judgment should temper his application of the various standards. Does the patient look overweight? Are there reasons for him to be slightly underweight by conventional standards? Is it psychologically or culturally sound for this person to strive for an ideal weight? For descriptive purposes in the classification of patients, two terms are appropriate — overweight and obesity. The adjective 'obese' is best restricted for those who are more than 15 percent above their ideal weight.

When it comes to the evaluation of the truly obese patient, the physician faces a complex problem. The

results of attempted weight reduction in this group are often disappointing while recurrence rates are substantial. Emotional symptoms and even psychiatric crises may be precipitated by too stringent therapy. Consequently it is of paramount importance to assess first the patient's personality, his motivations and his life situation. Considering these factors, is it likely that he will or even can accept and adhere to a diet? Is there a reason which is meaningful for him for undertaking a program of less food and perhaps more activity? Regarding emotional stability, three groups of obese persons have been delineated to serve as a guide in the evaluation of patients. There are those with poor food habits and little knowledge of food but who are stable psychologically; they have a good chance of success. A second group includes those with mild to moderate emotional problems, especially insecurity—when faced with tensions or problems, they overeat; this group may succeed but they will need a satisfying diet as well as emotional support and guidance in developing insight. The third group presents more serious emotional and psychiatric problems; they are unlikely to succeed and dieting may even be harmful through increasing guilt feelings, remorse and anxiety. Certainly for this last group weight reduction should never preceed psychiatric therapy.

IV Fad Diets

To be realistic, management must include an awareness of the public as well as the professional approach to this subject. There is probably no area of medicine where patients come to a physician's office with more information, with more notions and with a record of more attempts and failures. Obesity is a sensational subject in the lay press while fad diet products, health foods and other gimmicks represent a multi-million dollar business in North America today. The *current fad diets* include:

(i) *The minimal carbohydrate, high fat and protein group of diets* such as "The Drinking Man's Diet" and "The Air Force Diet" (although it has no Air Force sanction). These diets were ushered in by the misleading theme "calories don't count". Persons are told that it is not the number of calories which one eats but the kind—the restriction of carbohydrate to 40 to 60 grams daily allows one to eat as much protein and fat as desired without gaining weight and in fact weight should be lost regardless of the total caloric intake. However, it has been shown that many persons on these diets actually eat fewer calories than their customary intake due to the extra satiety value of high protein, high fat foods such as steak, eggs, cheese and milk. The concept that calories can be disregarded is based on the fact that fatty acid synthesis depends on a supply of reduced co-enzymes from carbohydrate metabolism; consequently with the amount of carbohydrate allowed in these diets it is unlikely that fat accumulation can take place. Furthermore on very high fat diets the rate of ketone formation in the liver often exceeds the capacity for their utilization for energy in the peripheral tissues, resulting in a ketosis which is usually mild and has the advantage of being anorexigenic. There is a risk of severe ketosis although the recommended intake of 40 to 60 grams of carbohydrate should prevent this development. Additional risks include atherosclerosis and deficiency of vitamins C and B complex since both of these vitamins are associated with foods consisting mainly of carbohydrate. The net effect of these diets, then, is threefold: reduction of fat synthesis, inefficiency of fat utilization for energy and, in many cases, a reduced caloric intake.

(ii) *The liquid formulae or the 900 calorie group* such as the Metrecal diet. These are nutritionally adequate but they lack bulk; furthermore, to prevent significant fatigue 1400 to 1500 Calories is generally considered to be the minimum for busy ambulatory males, while 1000 to 1200 is the lower limit advisable for active women.

(iii) *The egg diet* or the Mayo Diet (not authorized by the Mayo Clinic) is an example of diets in which the emphasis is placed on restricting oneself to a very few foods such as grapefruit, eggs and the like. These diets usually achieve a reduced caloric intake through the satiety value of foods such as eggs and through the temporary satisfaction which a patient may feel by adhering to a regimen which is unique enough to boast about.

(iv) *The 28 calorie or starvation diet*, known to physicians as the fasting approach. This diet has not been widely publicized in the press, but its use without medical supervision stems from the enthusiasm of patients who have been treated successfully in hospital and who then spread the news to friends. Fasting is discussed in detail later.

V Medical Management of Moderate Obesity

It is against this dramatic, highly powered approach that physicians must try to instill a little common sense into the subject of weight reduction. First of all a *long term approach*—lifelong caloric balance—should be the key concept in the management of overweight and obesity. Except for cases of extreme obesity or for special medical reasons, crash programs are not indicated. Efforts towards regaining or maintaining ideal weight must emphasize reeducation with respect to food selection, the end result being a new pattern of eating to which the patient will adhere for a lifetime. An enormous achievement will have been made if at the end of a period of weight loss, the patient knows he can eat any food, can eat anywhere and yet can maintain his desired weight. This is where fad diets, and to a lesser extent standardized low calorie diets, often fail. Both are apt to be regarded as only a brief interruption in one's usual food habits. The patient tires of the

special formula or of the special diet and returns to his old food habits. Usually little has been achieved.

To make the therapeutic effort worthwhile, the decision to lose weight must be given careful consideration. *Motivation* is the single most important factor. The decision to make the effort must be the patient's decision and for his reasons, although of course they may reflect an acceptance of both the physician's advice and reasons.

The next step is the establishment of a set of reasonable *goals* in terms of the extent and rate of weight loss. Two pounds per week is considered safe. This means a caloric deficit for the week of about 7000 Calories or 1000 Calories daily. Using a chart of recommended calorie intakes modified for age, this deduction is made. It should be emphasized that this is a flexible figure; strict calorie counting is not necessary although it may be employed at the initiation of the therapeutic program as an aid in the appraisal of food intake. The patient may be advised to prepare a chart or graph to remind himself of his goals and success in meeting them.

Instruction to the patient should include an explanation of the human caloric balance: caloric intake versus caloric expenditure through basal activities, physical activity and for growth, pregnancy and lactation if these apply. The effect of age on body function should be emphasized. It should be stated clearly that despite much that is still unknown about obesity, weight can only be gained when caloric intake is greater than expenditure and vice versa.

Exercise should be discussed before it gets lost in talk about food. Such factors as exercise tolerance, cardiorespiratory status, age, type of employment and socioeconomic status will all be considered in guiding the individual patient. It is important not to give a false impression about the effectiveness of exercise itself in weight reduction—one mile of walking uses only about 50 to 100 Calories while one hour of average walking consumes about 300 Calories. Mention can be made, however, of the other benefits of exercise—the development of muscles and the improvement of collateral circulation.

Finally *food*—the terms dieting and diet should be avoided as much as possible, because no one food or groups of foods needs to be eliminated nor does food intake need to be rigidly similar from day to day. Printed instructions may or may not be used; actually an inflexible, impersonal diet is less valuable than modification individually of the person's own food habits. The patient should strive to alter his food and caloric intake from day to day and from week to week on the basis of his own appetite, activity and weight record. There are two alternatives to a standard reducing diet: leaflets on weight control available free from government or commercial sources such as life insurance companies and Canada's Food Guide. The reason for recommending Canada's Food Guide in preference to standard low calorie diets is that the Guide is flexible enough to be adapted to the food habits of any ethnic group, it is simple enough for a child to follow and it provides between 1200 and 1600 Calories as well as an adequate amount of protein and all the essential vitamins and minerals. Two specific points need to be stressed about food. First, restriction of fat intake is more critical than carbohydrate since gram for gram there are nine Calories from fat and four from carbohydrate. The so-called hidden fats need to be noted—meats, cheese, salad dressings and so on. Secondly, the patient must learn to select the lower calorie foods within each part of the day's meals. This is where a calorie list or other dietary guide may be useful at first. In terms of ultimate success, the satiety provided by the day's food intake is important. To ensure this, several suggestions may be given: eat a protein food—egg, meat, fish, cheese or milk—at each meal; make meals more bulky by adding such foods as salads, clear soups and low calorie gelatin desserts; for inbetween meal snacks take tomato juice, tea, coffee or a calorie-free carbonated beverage; and for evening nibbling—celery, dill pickles and melba toast or bread sticks.

Many patients will want to use *artificial sweeteners.* If there is any reason for restricting sodium intake, they should be advised to chose the ones which do not contain sodium—calcium cyclamate for example.

Frequency of food intake and its relationship to weight control has been studied recently. It has been shown experimentally that large, widely spaced meals result in a greater degree of fat synthesis than do smaller more frequent feedings having the same total caloric value. It is stressed however that despite the increased fat synthesis in the former type of diet there is no difference in net weight gain or loss between groups on these diets provided that the diets are isocaloric. Nevertheless these findings may have relevance in human obesity, in which there appears to be a defective capacity for lipolysis. Thus increased fat synthesis, even when it occurs without net weight gain, is best to be avoided, being in some degree in the obese patient a one-way street. From these considerations has come the *nibbling* approach to dieting—six to ten small meals daily of 150-300 Calories each. The value of this approach has not yet been proved, but the opposite extreme in which the patient fasts all day only to eat a very large evening meal is definitely undesirable.

Followup of the patient is extremely important; it has been recognized that the physician's failure to follow such patients closely is often a key factor in the failure of therapy. Weekly office visits should be scheduled for the first month; thereafter every two weeks for the next two months and then monthly until a reasonable level of weight has been achieved *and* there is evidence that the patient is able to maintain this new level.

The individual physician's efforts may be supplemented by group therapy in which the team approach to management is utilized—those who may be included are physicians, nutritionists, psychiatrists and psychologists, and even athletic and beauty counsellors.

VI Additional Measures for the Seriously Overweight Patient

Simple management as just outlined may not be adequate by itself for the grossly obese patient. Here, history, physical examination and assessment of emotional stability and motivation are extremely important. *Long term* realistic goals should be discussed. An initial period of *hospitalization* is often advisable for a number of reasons: the enforcement of a 400 to 800 Caloric intake will demonstrate to the patient that weight loss is possible for him; fluid balance may be observed; cardiac, respiratory, renal and liver function may be assessed as any of these systems may be involved in the aftermath of extensive fat accumulation; a trial of fasting may be used in selective cases; and finally drugs may be introduced.

Fluid balance studies may show a tendency to fluid retention during weight reduction. Since the oxidation of 100 grams of fatty acids yields 112 grams of water, failure to excrete this water will obscure any weight loss. The actual weight relationship is 1¼ pounds to 1 pint of water. In cases where a positive water balance is suspected or proven, water intake may be restricted to one pint daily from all sources, while salt restriction may be employed as a further measure. Lastly, diuretics can be given (e.g. a thiazide three times weekly).

Total fasts either as an initiation to weight loss or intermittently during periods of weight reduction may be used. The average duration of an individual fast is seven to 14 days. The main benefit is apt to be a psychological one, since balance studies have shown that actual weight loss is at the expense of lean body mass —approximately two-thirds is from lean tissue and only one-third from adipose tissue. During the actual fast only calorie-free liquids and a multi-vitamin and mineral preparation are given. Exercise is minimal. Acceptance of this regimen is bolstered both by the satisfaction of actually losing weight and by the prompt development of anorexia. A mild degree of euphoria is common while depression is rare. The *metabolic complications* are ketosis which is usually mild, and a tendency towards hyperuricemia; checks for ketones should be done daily and for serum uric acid weekly. Uricosurics are necessary only for those with a gout predilection. There is the added risk of a sodium depletion syndrome manifested by weakness, light-headedness and nausea, and serum sodiums should be done once or twice weekly and the sodium intake adjusted accordingly. Atrial fibrillation and flutter may also appear. *Contraindications* include uncontrolled or labile diabetes mellitus, pregnancy, recent coronary infarction, acute infection and acute hepatic disease. The proponents of this method warn against indiscriminate use of fasting; like major surgery or potent drugs, it should be employed with a high degree of selection and never without close supervision. The use of fasts has brought success among groups of obese persons who were previously considered to be refractory to the usual clinical approaches; for example in one group, 50 percent continued to lose satisfactorily on a low caloric diet after the initial indoctrination and with continued and progressive instruction and encouragement.

Drugs have been left to the last because the consensus is that they have at the most a secondary role in weight control. (i) *Thyroid extract* is perhaps the most controversial. The aim in thyroid therapy is to render the patient slightly hyperthyroid. Because endogenous thyroid secretion is soon suppressed by the introduction of exogenous hormone, thyroxine must be given in dosage slightly greater than the normal (equivalent to 0.15 to 0.3 mg. thyroxine daily) endogenous secretion rate in order to achieve the therapeutic aim. The preferred method is to start with 1.0 milligram L-thyroxine daily and gradually lower this to about 0.4 milligrams daily. It should be continued for six months to a year and should then be withdrawn slowly to allow endogenous production to take over again. The effects of thyroid are an increase in basal metabolic rate due to its accelerating effect on tissue metabolism. However it may increase losses of lean body mass rather than adipose tissue. Side effects which may appear are tachycardia, palpitations, nervousness and insomnia. For these reasons the patient must be followed closely especially at first; indeed it is advisable to commence administration in hospital, if possible. Thyroid may have the additional benefit of acting as a mild antidepressant through increasing activity and it can be a useful adjunct for the poorly motivated patient. In this context it is considered preferable to the appetite depressants, since thyroid lacks the addictive properties of the amphetamine group. (ii) *Anorexigenic agents* are used far too often as a crutch, and failure soon ensues with the development of tolerance, usually in about four to six weeks. Furthermore they become another addiction for the patient who is already addicted to food. Nevertheless they may be used on rare occasions as an aid in initiating the process of weight reduction. The current anorexigenic agents—the sympathomimetic amines and amphetamines—act chiefly by stimulating the hypothalamic satiety centres. Side effects include irritability, insomnia, dry mouth, constipation, restlessness, tachycardia and the potentiation of cardiac arrhythmias. The dose of the amphetamines is 5 to 20 milligrams daily. (iii) *Antidepressants* may also be required in difficult cases where there is an associated psychiatric problem.

It is fitting to conclude with these words from one of America's most experienced and most respected workers in the field of weight control: "Not all obese persons

should undertake weight reduction; only those for whom there is some likelihood of success and on whom undesirable sequelae are unlikely should be encouraged to reduce. A reasonable well-adjusted individual, with a meaningful reason for losing weight and good environmental circumstances, can succeed if the therapist is willing and able to give unjudging, unchastising, unthreatening, sympathetic support with sound dieting advice in frequent contacts over a period of time. The roots of the obesity problem are psychological, sociological, cultural, economic and physiological. Prevention is the only real answer." (Young)

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Relationships Between Obesity, Diabetes Mellitus, And Hypertension

D. Rapoport, 6T7

INTRODUCTION

Obesity, hypertension, and diabetes mellitus occur together in pairs and as a triad very frequently. For example, 50 to 70% of adult diabetics are obese, five times the prevalence of obesity in the non-diabetic population. Among obese, up to 60% have an abnormal oral glucose tolerance test, and many hypertensives also demonstrate decreased glucose tolerance. In obese-hypertensives the incidence of diabetes in very high. As a further example, in one series of 5000 adult hospital patients, there were 589 with diastolic hypertension, and 213 with diabetes. Of the diabetics, 24.6% had hypertension and 54% were obese. Of the hypertensives, 11.5% had diabetes and 34% were obese. Of importance is the fact that of 57 patients with both diabetes and hypertension 86% were obese.

The ultimate significance is this: obesity seems to be the most important predisposing factor for the triad. The occurrence of serious vascular disease is hastened by the triad or any member of it. Among obese persons, the incidence of death from diabetes is increased 3½ times, the incidence of death from heart disease is increased twofold, and the incidence of death from cerebral vascular disease is also increased. It is also true that obese diabetics are often resistant to treatment with insulin, while obese hypertensives often resist treatment with antihypertensive agents. The treatment of choice is weight reduction. With effective weight control, both adult diabetes and hypertension can be helped.

Relationships between obesity, diabetes mellitus, and hypertension, and the intriguing problem of whether obesity "causes" diabetes and hypertension, or whether the reverse is true, will be discussed here.

1. OBESITY AND DIABETES MELLITUS

Diabetes of maturity onset has been thought to be largely a penalty of obesity. Up to 60% of obese persons have an abnormal oral glucose tolerance test, and many have pancreatic islets that are hypertrophied and hyperplastic. There seems to be a very good case for the theory that obesity leads to diabetes. The overweight patient consumes more carbohydrate, giving him excess substrate on which his insulin must act, so he develops an adaptive hyperinsulinism which is difficult to maintain. He is less active—this in itself harms glucose tolerance. There is evidence that 30-60% of obese persons have increased adrenocortical function, and this too is diabetogenic.

The most recent evidence, however, suggests that diabetes may cause obesity, rather than the reverse. Diabetes mellitus can be divided into the insulin dependent variety seen in children, and the non-insulin dependent type seen in adults with maturity-onset disease. (Table 1). The metabolic abnormalities that result in obesity are related to the etiology and pathogenesis of diabetes. Lipogenesis occurs chiefly through the oxidation of glucose by the pentose pathway, producing TPNH which supplies hydrogen for the reduction steps in lipogenesis from acetyl Co-A. Lipogenesis also requires the continuous generation of glycerophosphate, derived entirely from carbohydrate, to serve as the intracellular esterifying acceptor for newly formed fatty acids, allowing the formation and storage of neutral fat. Thus *active glucose utilization must occur* for obesity to develop, as lipogenesis proceeds very quickly here. Also *lipogenesis cannot occur in the absence of insulin,* as carbohydrate utilization depends on an adequate supply of it. Accordingly, juvenile diabetics, with little or no insulin, have a lipolysis that can become severe, while adult-onset diabetics with normal or high levels of insulin can become obese. As stated above, adult diabetics are little helped by the administration of insulin—in fact, one can see from the above considerations that insulin may promote obesity in them.

Various factors must, therefore, he considered in the complicated relationship between obesity and diabetes:

TABLE 1

Insulin Dependent (Juvenile) Diabetes	*Non-Insulin Dependent (Maturity-Onset) Diabetes*
1. circulating blood insulin decreased or absent	1. circulating blood insulin normal or elevated
2. very labile, fluctuating blood fatty acids	2. stable but elevated blood fatty acids, elevated triglycerides
3. ketosis develops easily without exogenous insulin	3. resistant to ketosis, rarely develop negative protein balance
4. striking capacity to lose weight if poorly controlled	4. persistent obesity in many that often resists treatment
5. treated with insulin	5. often resist insulin treatment. Treat by weight reduction.
	6. frequent premature atherosclerosis and vascular complications

A. *Insulin Antagonism*—An albumin-bound antagonist exists to the action of insulin, rising in titre as the disease progresses. Called *synalbumin*, it is a low molecular weight compound, probably a polypeptide, and possibly the B-chain of the insulin molecule itself. It may be inherited as a Mendelian dominant. The pituitary-adrenal axis seems to be in some way a factor, as the presence of synalbumin depends on the presence of the pituitary and adrenal glands.

It is important to note that synalbumin is antagonistic to insulin only on striated muscle, *not on adipose tissue*, so it does not harm glucose utilization for lipogenesis. This might explain the obesity of some adult diabetics—*prediabetes may lead to obesity*. Juvenile diabetics have almost no insulin. They too have an insulin antagonist in their blood, but perhaps the pancreas in this condition cannot compensate due to the added diabetogenic factor of growth. Without insulin they lose weight. Looking even earlier in the life history of diabetes, it is important to note that synalbumin can cross the placental membranes. This might explain the obese newborn infants of diabetic mothers, who are often born with hypertrophied islets.

This antagonist is present in normal persons in low concentration, but is elevated in prediabetes, obese diabetes, and some grossly obese non-diabetic persons, as well as poorly controlled or untreated insulin-needing diabetics.

There is another theory to explain insulin non-antagonism in fatty tissues. It states that much blood insulin is bound and inactive, and in diabetics can be split by adipose tissue, but not by muscle tissue.

B. *Free Fatty Acids*—In obese persons, free fatty acids of blood are elevated and do not fluctuate normally with feeding and fasting. It has been shown that elevated free fatty acid levels inhibit phosphokinase enzymes, and so the phosphorylation of glucose. Thus glucose oxidation is decreased in the skeletal muscle of obese persons. Accordingly, free fatty acid elevation may contribute to the insulin resistance in obesity.

C. *Hormones*—Diabetes is definitely influenced by the pituitary-adrenal system. *Growth* hormone in particular has been implicated as a factor in diabetes. It is known to be diabetogenic, and although it is usually lipolytic, depot fat can still be deposited in its presence if food intake is high. Growth hormone levels have been reported high in some obese diabetics, but most studies indicate that there is *not* an elevation of baseline levels of human growth hormone in obese subjects. This would suggest that the peripheral antagonist noted above is not growth hormone.

At any rate, insulin insensitivity in obese persons may well be a polyendocrine phenomenon. The frequency of "stress" diseases in diabetes, including obesity, hypertension, atherosclerosis and cholelithiasis, points to the adrenal gland.

D. *Hypothalamus*—Both obesity and diabetes mellitus are linked to hypothalamic function, and each can be produced by injury there. In mice, hypothalamic injury produced by gold thioglucose (supposedly affecting the glucose-sensitive satiety centre) will cause obesity, and in a few of these hyperglycemia is noted. In general, obesity can be caused by hypothalamic injury alone, but some additional endocrine activity is needed for diabetes to occur as well. This was evoked in mice, pretreated with gold thioglucose, by exposure to cold and stress.

TREATMENT OF OBESITY-DIABETES

The first step in the treatment of obesity-diabetes is weight reduction, the dictum being "Treat the obesity before the diabetes. Manage the obesity and you manage the diabetes." In many cases a weight loss of only 5 to 10 pounds will produce satisfactory control of the diabetes and restore the oral glucose tolerance to normal, though the cortisone stressed glucose tolerance may still be abnormal, indicating a residual anomaly.

Unfortunately, weight reduction may be difficult in an obese diabetic. Low caloric diets and anorexigenics such as phenmetrazine HCl are suggested. Oral anti-diabetic agents should be avoided until after weight reduction has been attempted.

2. OBESITY AND HYPERTENSION

Obesity-hypertension is extremely important and common clinically. In one series 34% of hypertensives were obese. Since many obese persons are not hypertensive and many hypertensives are not obese, the relationship is probably one of association rather than of cause and effect. Hence one should look to the environment for an etiology. In our culture there are at least three factors which have favoured the occurrence of obesity-hypertension.

A. *Decreased Acitvity*—Failure to exercise is a factor in both obesity and hypertension. In the absence of adequate exercise the appetite is no longer a reliable guide to nutritional needs and eating to satiety now often involves over-eating. Formerly, one would eat according to his energy output.

B. *Stress*—This factor is certainly the most difficult to define or to alter. Steroid hormones can cause or aggravate either condition, as in Cushing's syndrome, where diabetes occurs as well. A "failure in adaptation" to stresses in our environment could be implicated.

C. *Diet*—This is probably the most important factor. Diet has changed greatly over the past one hundred years. Most common foodstuffs now are palatable, concentrated, and highly digestible, in contrast to the bulky fare of the past, consisting to a large extent of bread. Much more *fat* is now consumed, in England the comparable figures being 140 grams daily per person today and 30 grams in 1835. The ability to separate *sugar* has been responsible for a vast increase in sugar consumption, and has contributed to obesity (excess sugar is deposited as fat), diabetes, and probably coronary thrombosis. The high *salt* content of our food is undoubtedly

a factor in the etiology of hypertension. Since salt is important in hypertension, and calories in obesity, one must assume that the obese person consumes excess salt as well as calories if he becomes hypertensive. To test this hypothesis one author subjected obese hypertensive subjects to either prolonged drastic caloric restriction, or to prolonged drastic salt restriction. Caloric restriction without salt restriction did not lower their blood pressure, while salt restriction without caloric restriction did lower it. Some animal research shows that hypertensive animals will not develop atherosclerosis, even on an "atherogenic" diet, unless salt is added. This again emphasizes the role of salt in hypertension and its complications. As regards the fat metabolism of hypertensives, up to 60% of hypertensives have elevated triglycerides and cholesterol, and some authors report a fall in these levels on antihypertensive therapy. Still, the relationship is not clear cut. Many normal persons have elevated serum lipids, and most agree there is no correlation between hypertension and elevation of serum lipids.

TREATMENT OF OBESE-HYPERTENSION

The first step is weight reduction. Many mild hypertensives are rendered normotensive by weight reduction alone. Failing this, one resorts to rest, sedation, salt restriction, thiazide diuretics and finally antihypertensive drugs.

3. HYPERTENSION AND DIABETES MELLITUS

Many hypertensives are prone to diabetes, especially if they are obese as well. The reverse is just as true—many diabetics are hypertensive. In one large series 24.6% of diabetics had hypertension, and 11.5% of hypertensives were diabetic. Systolic hypertension has a good explanation in diabetes: premature atherosclerosis. Diastolic hypertension is also more common, however. Pyelonephritis and the Kimmelstiel-Wilson lesion account for some cases among severe diabetes, as could the prevalence of obesity. However, the excess is not solely due to obesity, though hypertension seems to be concentrated in overweight persons with *mild* diabetes.

A. *Serum Lipids*—As stated above, up to 60% of hypertensives have elevated triglycerides and cholesterol. It is notable that increasing triglycerides decreases CHO tolerance and increases the danger of atherosclerosis. In fact, knowledge of a hypertensive's diabetic status as revealed by his oral glucose tolerance test is at least as important as determination of his blood pressure in assessing the risk of coronary infarction.

B. *The Potassium Ion and Hypertension-Diabetes* — An interesting group of hypertensives have a decreased total body potassium. This occurs chiefly in cases of primary aldosteronism, either hypo- or normokalemic, and less often in cases of renovascular hypertension with secondary aldosteronism. Among these patients, carbohydrate tolerance is often impaired. It seems that potassium lack causes a decrease in endogenous insulin production, and an inability to release insulin quickly when needed. Insulin release curves here are similar to those of maturity-onset diabetes: after a glucose load, the rise in blood insulin is slow. The curve can be normalized if potassium supplements are given first. The importance here lies in the fact that diabetes and hypertension can occur together for a very good metabolic reason, and in this case both are surgically curable, by repair of renal artery stenosis or removal of adrenal adenoma.

Conn believes adrenal adenomata account for 15% of so-called "essential" hypertension, and that half of these cases are diabetic. In his opinion, many cases of "maturity-onset diabetes" with hypertension are in reality cases of primary aldosteronism with reversible diabetes. Therefore, he suggests that potassium supplements be given to suspicious cases. If the oral glucose tolerance test improves after serum potassium rises, primary aldosteronism becomes a strong diagnostic possibility.

CONCLUSIONS

Obesity, diabetes mellitus and hypertension are very common today. They occur together more frequently than is commonly realized.

While obesity is diabetogenic, evidence is also presented that diabetes can lead to obesity. Insulin antagonism effective in muscle tissue but not adipose tissue is the explanation of the latter. Free fatty acids are elevated in obesity, and they are known to decrease carbohydrate tolerance. Hormonal effects and the hypothalamus may play a part in the syndrome of obesity-diabetes. The first step in treatment is weight reduction.

Obesity-hypertension is very common. Environmental factors are implicated. These are decreased activity, stress, and diet. Dietary changes, chiefly in the form of increased fat, sugar, and salt content, appear to be involved in the increased incidence of obesity, diabetes mellitus and hypertension. Once again, obese-hypertensives are treated first by weight reduction.

The coincidence of hypertension and diabetes can be partially blamed on the prevalence of obesity in each. Knowledge of a hypertensive's glucose tolerance is important in assessing his risk of cardiac infarction. Hypokalemia, as seen in primary aldosteronism (Conn's syndrome) and secondary aldosteronism (renovascular hypertension), can cause impaired glucose tolerance. In these latter two cases the diabetes can be helped by potassium repletion or by surgery. Hypokalemia may be the key in cases of hypertension-diabetes and should not be ignored.

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Student Research

New Thoughts In Diabetes: Insulin Antibodies, Microangiopathy, And Autoimmunity

Some of the newest thoughts in the vast unknown of diabetes today are coming from the field of Immunology. Exploration and research here are just beginning, but already, as will be seen, several interesting discoveries have been made.

I Insulin Antibodies

It has become evident from many recent papers that virtually all subjects, whether diabetic or not, who receive insulin form antibodies against it, the quantity of antibody varying greatly from individual to individual. It is also known that in response to a single antigen, more than one type of antibody can be formed. On antigenic stimulation by exogenous insulin, 3 different kinds are produced (Table 1).

(i) *Anaphylactic antibody*—a relatively recent discovery. It has been reported in many species and is known by several names—anaphylactic antibody, skin sensitizing antibody, and mast-cell-sensitizing antibody. Its properties vary slightly from species to species and in man it has reagin-type characteristics.

The mechanism of action of this antibody is fairly well established in the guinea pig, and it is most likely similar in other species. A clue is given by one of its alternate names, mast-cell-sensitizing antibody. This antibody attaches itself to mast cells in the skin, respiratory tree, and other parts of the body, and on being challenged with antigen forms antigen-antibody complexes which somehow cause degranulation of the cells, with release of histamine and the production of increased capillary permeability and vasodilatation.

(ii) *Neutralizing antibody* — may be demonstrated and measured very easily by showing that serum can inhibit the effect of insulin, firstly *in vivo* by protecting mice against hypoglycemic convulsions, and secondly *in vitro* by the prevention of a characteristic metabolic effect of insulin on living tissues, such as the inhibition of net glycogen synthesis by the mouse hemidiaphragm.

(iii) *Binding Antibody*—as yet uncertain whether this type of antibody is actually a separate entity or whether it is identical with the neutralizing antibody. However, it is most probable that there does exist an antibody which can bind insulin and yet *not* neutralize its effects.

One very important question arose when insulin antibodies (to exogenous insulin) were first demonstrated, and indeed this question plagued the entire research effort until as recently as 7 years ago. Is the antibody an antibody against insulin itself or is it an antibody against some impurity in the insulin preparation? The answer was provided by a relatively simple experiment in which it was shown that insulin could be recovered from precipitated antigen-antibody complex by enzymatic digestion, thus proving insulin to be the antigen.

II Clinical Manifestations of Immune Response to Insulin

Two types of immune response have been fairly well established. These are insulin allergy and insulin resistance.

(i) *Allergic reactions* can be either local or general. Locally, there is a dermal reaction at the injection site, characterized by a burning or itching, followed within a few hours by erythema and induration. The incidence of these reactions in human diabetics is approximately 50% in most surveys. This type of sensitivity occurs during the first 3 months of insulin therapy, most often after a week or two, and usually disappears after a few

TABLE 1

anaphylactic antibody	*neutralizing antibody*	*binding antibody*
migrates with beta globulins	migrates with γ globulins	?
IgA (γA) or ?IgE	IgG (γG)	?
7-10s	7s	?
thermolabile	heat stable	?
sensitizes skin (Prausnitz-Küstner test)	precipitates insulin and neutralizes effects of insulin	may be measured and demonstrated by hemagglutination, inhibition of complement fixation, immunoprecipitation and binding of I^{131} labelled insulin

weeks or months of continuous treatment, which has the effect of desensitizing the patient. The general reactions occur much more rarely, and fortunately so. They consist of (a) generalized urticaria, (b) angioneurotic edema, or even (c) anaphylactic shock. Such reactions most commonly follow shortly after the reinstitution of insulin therapy after a period of omission. The antibody for the allergic reactions, both local and general, is the anaphylactic antibody.

(ii) *Insulin resistance* is the condition in which more than 200 units of insulin are required daily to control the diabetic. If between 60 and 200 units are needed, the patient is insulin insensitive or hyporesponsive. The etiology of insulin resistance can be either primary or secondary. The secondary type occurs when the diabetes is associated with certain other disease states, for example, infections, some endocrine disorders (eg. thyrotoxicosis, adrenal cortical hyperfunction), impaired liver function (eg. cirrhosis, hemochromatosis), and chronic lymphocytic leukemia. The underlying mechanism in most of these cases is obscure, but increased gluconeogenesis, anti-insulin factors other than antibodies and a decreased sensitivity of muscle and adipose tissue to insulin have all been postulated. Primary insulin resistance occurs in diabetics in the absence of other disease. Except for a very few cases, the serum from patients in this category contains high levels of either binding or neutralizing antibodies. As mentioned, almost all insulin-treated diabetics have antibodies in their blood. Fortunately, however, only a few of them develop high enough titres to become insulin resistant. Resistance occurs in approximately 1 in 1000 insulin-treated diabetics. In resistant patients significant insulin action is not achieved until the hormone is injected in excess of that required to saturate the binding sites of the antibodies. In many patients this may take up to a thousand units of insulin or even more daily. These patients are also more difficult to control.

Various types of insulin are employed today to treat the diabetic, but the one most commonly used is Bovine Insulin. Patients becoming resistant to this insulin would be expected to have high titres of antibody directed specifically against Bovine Insulin, and would be expected to be more sensitive to Pork Insulin. Clinically, it has been observed that in many cases these patients actually *are* sensitive to Pork Insulin. However, it is not so in every case. To determine whether this change *will* benefit a given patient, a simple laboratory test was recently devised which determines the relative amounts of bovine and pork insulin which can be bound by the patient's serum antibodies. A simple formula is then applied to predict the effectiveness of pork insulin. There is a striking difference in the reactiveness of the antibody to Beef Insulin from patient to patient. In one study, of 15 sera tested, only 7 had a greater affinity for Beef Insulin than Pork Insulin. Clinically 6 of these 7 patients responded well to Pork Insulin—the seventh not having been tried. A closer agreement between laboratory and clinical findings cannot be achieved. This test should be done wherever facilities are available.

Another recent discovery promises to aid in the treatment of insulin-resistant diabetics. This is Sulfated Insulin, an altered form of insulin which is less readily neutralized by a given amount of antibody and which is also less antigenic than unaltered insulins. It can be seen in Table 2 that in 3 hyporesponsive (60-200 Units of insulin daily) and 8 resistant patients, the dose of Sulfated Insulin effective in controlling the diabetes was 1/10 to 1/5 of the dose of unaltered insulin. Moreover, the patients were more easily controlled. This was especially emphasized by the 2 cases H.M. and F.H. in whom, when treatment with Sulfated Insulin was interrupted, control could not be maintained even with much larger amounts of standard insulin. When Sulfated Insulin therapy was resumed, control was re-established. Another significant finding was that there was no evidence of an antigenic stimulation by the Sulfated Insulin, as no increase in dose was needed, even after more than 2 years of continuous therapy. A more recent study has been carried out comparing Sulfated Insulin with the more commonly used insulins—regular, protamine zinc, lente, & NPH—in twenty-four hospitalized diabetics. For six severe ketosis-prone diabetic patients, Sulfated Insulin in approximately equal doses failed to control the disease, as did the usual long-acting insulins. For four mild diabetics Sulfated Insulin showed no advantage. However, for nine of twelve moderately severe diabetics, Sulfated Insulin in less or equal amounts provided better control. Furthermore, in two insulin resistant patients, Sulfated Insulin very greatly decreased the insulin requirements (to 5% and 37%) and gave much better control. Moreover, hypoglycemic reactions were no more frequent and there were no important toxic effects. The authors suggest that perhaps a stable, longer acting Sulfated Insulin (eg. Protamine Zinc Sulfated) might be even more useful for the moderate diabetics and might even control the severe group.

III Insulin Antibodies and Microangiopathy

Thickening of capillary and other basement membranes together with endothelial proliferation are characteristic and consistent early findings in diabetics. In fact they sometimes antedate the appearance of chemical diabetes and certainly antedate the complications seen clinically. This sequence has been reported by many observers. The areas of the body involved are widespread, including the retina, kidney, skin, vasa nervorum, vasa vasorum, islets of Langerhans, muscle capillaries, and even the placenta of diabetic mothers. The common factor in most, if not all, the lesions of diabetics is believed to be diabetic microangiopathy. That it explains the retinopathy, nephropathy, and many cases of gangrene is fairly well established. Many also believe that the neuropathy can be explained by changes in the walls of the vasa nervorum. Perhaps even

TABLE 2
PATIENTS TREATED WITH SULFATED INSULIN

PATIENT			DAILY INSULIN REQUIREMENTS		DURATION OF TREATMENT WITH SULFATED INSULIN (*months*)
Name	*Age (yrs.)*	*Sex*	*Unaltered (units)*	*Sulfated (units)*	
J.B.	68	M	70	5-15	27
H.M.	60	F	150	30	26
Y.C.	61	M	180-200	36	32
M.T.	14	M	200-300	40	24
M.D.	72	F	300	25	3
E.J.T.	69	M	300-530	25	14
M.R.	49	F	330	50	5
M.D.T.	72	M	250-500	60	34
M.K.	52	M	550	63	11
J.R.G.	45	F	450-500	90	20
F.H.	57	M	2000-3000	135-200	27

the accelerated rate of atherosclerosis can be blamed on the alterations in the vasa vasorum. It is also likely that the basement membrane and other changes may impair the delivery of insulin from the Beta-cells to the target cells. This is not difficult to see (Figure 1) when one realizes that before an insulin molecule reaches its target it must traverse the basement membrane of the islet, a space, the basement membrane of the capillary, a space, the endothelial cytoplasm, and then the endothelial cytoplasm again, a space, the capillary basement membrane, a space, and in most target tissues at least one more basement membrane.

What is the pathogenesis of diabetic microangiopathy? It has been stated already that the microangiopathy may antedate the metabolic derangements seen clinically. Patients may even present with gangrene of their toes or with extreme nephropathy, retinopathy, or neuropathy without knowing they have diabetes. Furthermore microangiopathy is seen in the young patient as well as the old, and in the carefully controlled as well as the neglected. It is probable that the vascular phenomena are an integral part of diabetes rather than a complication of this disease. Staining procedures, chemical studies, and electron microscopy all indicate that the changes in the various structures—basement membranes, hyalinized islets, and retinal microaneurysms and exudates—have a similar composition. These investigations strongly suggest that an antigen-antibody reaction, with insulin as the antigen, is responsible.

The first type of evidence derives from fluorescence microscopy. The lesions have been shown to bind specifically fluorescein-conjugated insulin and fluorescein-conjugated anti-human globulin. The following study on the glomeruli of diabetics and non-diabetics is just one of the many that stress this finding (see Table 3). In the diabetic group there was a high percentage of insulin and anti-human globulin binding. In the other patients there was no insulin binding. However, some binding was observed with anti-human globublin, all cases of which (except one with malignant hypertension) are believed to have an immunological component. Another significant finding is that of the 25 diabetics in group 1, 3 had never been on insulin therapy. Similar results have been observed in the retina, hyalinized islets, and other tissues.

Secondly, electron microscopists have demonstrated a fibrillar material in the hyalinized islets. Similar material is also seen in the thickened basement membranes all over the body. Structurally it is similar to aggregations of antigen-antibody complexes.

Another type of finding which provides added strength to the thesis that the angiopathy of diabetics is related to an immune reaction is as follows: Rabbits immunized with an insulin-adjuvant mixture over a 30 month period are then challenged with small doses of insulin every other day for 6 weeks. Postmortem examinations then done disclose proliferative vascular lesions, nodular glomerulosclerosis, hyalinized islets, and even retinal microaneurysms. Furthermore, all of these bind fluorescein-conjugated insulin and anti-rabbit globulin. They thus seem to be the same as the human lesions.

Fourthly, the high frequency of proliferative vascular disease in diabetics itself supports an immune concept, because these lesions are often seen in various other disease states, such as chronic glomerulonephritis, systemic lupus, rheumatoid arthritis and occasionally in association with the malignant tumors; conditions (especially the former three) considered by many to be a result

of immunogenic mechanisms. Moreover, these lesions are also seen in animals immunized with a variety of differenent antigens.

A final piece of evidence comes from the more recently described exudative lesions seen in the more advanced diabetic kidney. They are characterized by deposits which have been shown to contain gamma-globulin. Similar lesions also occur in the collagen diseases.

Thus, there is evidence that diabetic microangiopathy is caused by an immune reaction to insulin. In most cases the insulin has been exogenous insulin. However, there are reports, as the one we have seen, that insulin-binding lesions do occur in patients who have never received insulin therapy.

IV Diabetes—An Autoimmune Disease?

This brings us to probably the newest direction of thinking in diabetes. Is it an autoimmune disease? The evidence is far from conclusive, but there are workers who have put forth many pursuasive arguments on this behalf:

(i) Insulin and anti-human globulin do bind to lesions in diabetics previously untreated with insulin.

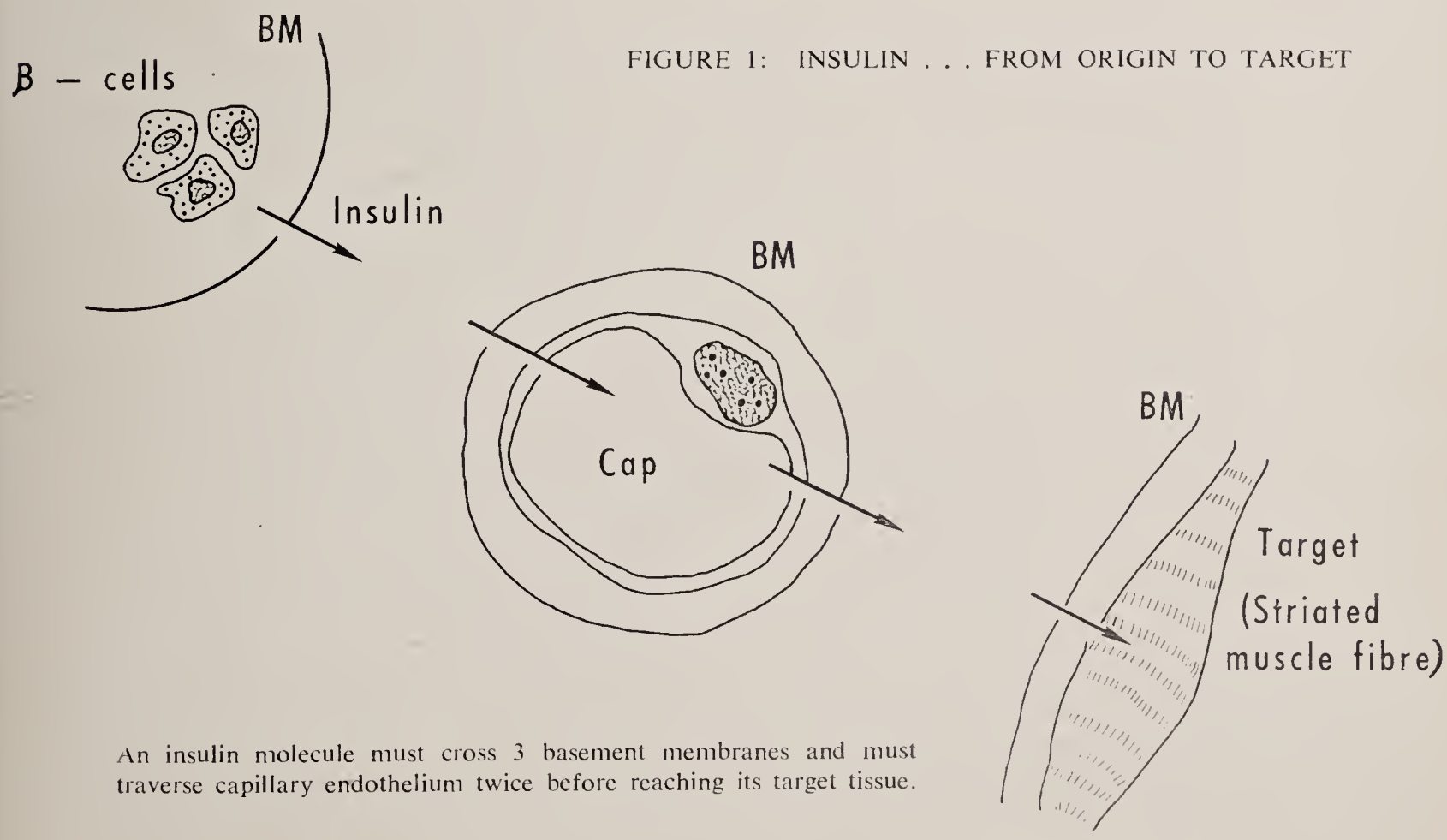
(ii) Insulin antibodies have now been demonstrated in the sera of some diabetics previously untreated with insulin, by the sensitive complement-consumption test.

(iii) It has been shown that insulin antibodies can actually produce the picture of diabetes. By immunizing and later challenging rabbits, some workers have mimicked the microvascular lesions in diabetics, as has been previously stated. Furthermore, the injection of guinea pig anti-ox insulin serum into mice neutralizes the hormonal action of the endogenous mouse insulin and produces the metabolic findings of diabetes, including weight loss, glucosuria, and ketonuria. As a

TABLE 3
INSULIN-BINDING CAPACITY OF GLOMERULI BY FLUORESCENCE MICROSCOPY

GROUP	Insulin		Anti-human globulin	
	No. cases	% positive	No. cases	% positive
Diabetic Nodular Glomerulosclerosis	25	96.0	25	48.0
Diabetic Without Glomerular Disease	16	18.8	16	12.5
Pancreatic Disease	2	0	2	0
Non-Diabetic Diffuse Glomerulosclerosis	2	0	2	0
Renal Amyloidosis	7	0	7	28.6
Myeloma Nephropathy	5	0	5	80.0
Lupus Erythematosis	3	0	3	66.7
Glomerulonephritis	4	0	4	0
Arteriolar Nephrosclerosis	19	0	15	6.7
Chronic Pyelonephritis	4	0	4	0
Normal Kidneys	10	0	5	0
TOTAL	97		88	

FIGURE 1: INSULIN . . . FROM ORIGIN TO TARGET



An insulin molecule must cross 3 basement membranes and must traverse capillary endothelium twice before reaching its target tissue.

matter of fact, this technique is now being used commonly to produce diabetes in the experimental animal because of definite advantages it has over the alloxan method.

(iv) Another area of investigation is the field of gerontology, in which there is much interest in the theory of mutations of immunologically competent cells with aging and the production of autoimmune diseases. It is also possible that mutations may occur in other somatic cells, such as the pancreatic Beta-cells, thus forming an altered insulin which would then act as an antigen eliciting antibody formation and causing diabetes. Compatible with such a view is the observation that glucose tolerance decreases with aging even in individuals who do not developed clinical diabetes. In addition it would also account for the insulin-binding reactions in individuals who have never received therapeutic insulin.

(v) Lastly, some have suggested the possibility of an autoimmune mechanism based on the reports of an "insulitis" in the islets of early juvenile diabetics. This consists of a lymphocytic infiltration, occurring in some instances before insulin therapy. It is very similar to lymphocytic thyroiditis, a disease considered by many to be an autoimmune phenomenon.

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Hyperlipoproteinemia

K. Pritzker 6T7

Lipid in the blood can be found either free as cholesterol and free fatty acids or bound to protein as protein-triglyceride-cholesterol particles in the form of chylomicrons, betalipoproteins, pre-betalipoproteins, alphalipoproteins. The blood concentration of these lipids is an index of the equilibrium of fat metabolism.

Fredrickson has classified the hyperlipoproteinemias on the basis of serum morphology—the concentration of cholesterol and triglyceride by biochemical analysis, and the concentration of chylomicrons, betalipoproteins, pre-betalipoproteins, and alphalipoproteins by paper electrophoresis. This classification is arbitrary in that mixed types and types beyond the classification are being discovered as analytical methods improve, but it is valuable in that it demonstrates that there exist several heterologous disorders within this group—each with its own management and prognosis. Most of these disorders are familial although the modes of their inheritance are unsettled.

Type I: Hyperchylomicronemia

These patients have a creamy plasma with markedly elevated chylomicron concentration as well as increased plasma cholesterol and triglycerides. Post-heparin lipolytic activity (PHLA) is often low suggesting that decreased lipoprotein lipase activity may be responsible for chylomicron accummulation. This disease usually presents in childhood and may present with episodes of bizarre post-prandial abdominal pain. Hepatosplenomegaly secondary to fat phagocytosis by the reticuloendothelial system may be evident. Pancreatitis is a common complication of this condition. Definite evidence of premature atherosclerosis has not been found in this group. As this disorder is manifest by excess exogenous fat in the circulation, treatment involves limitation of fat intake and limitation of intake to low and medium chain fatty acids in order to minimize chylomicron formation.

Type II: Hyperbetalipoproteinemia = essential familial hypercholesterolemia

This autosomal recessive disorder is characterized by extremely high cholesterol levels, elevated betalipoproteins, and a clear plasma. Triglyceride levels, PHLA and glucose tolerance tests are normal. These patients suffer the effects of markedly premature atherosclerosis. The diagnosis is facilitated by the presence of xanthomata in skin, tendons, and mucous membranes, xanthelasma, arcus senilis, and lipid and carotene deposition in the palmar creases. Treatment is directed toward impairing both fat absorption and utilization. Low cholesterol, unsaturated fat diets as well as bile salt binding (thereby inhibiting fat absorption) by cholestyramine are employed. As a heroic measure, resection of the terminal ileum to reduce bile salt resorption has been tried. None of these measures have been successful as yet in controlling atheroma formation in these patients.

Type III:

Elevated betalipoprotein, pre-betalipoprotein, cholesterol and triglyceride levels are found in the sera of these patients. These people possess a raised insulin-like activity in their blood as well as an abnormal tolbutamide glucose tolerance test. They are prone to xanthoma and premature ischemic heart disease. There may be a family history of mild diabetes. An increase in fat synthesis from glucose is thought to be involved in this disorder; therefore, reduction of dietary carbohydrate is the current treatment.

Type IV:

These patients have a high pre-betalipoprotein concentration in the presence of normal or only slightly elevated cholesterol, triglyceride and uric acid levels. Eruptive, planar and tendon xanthomata are commonly present in conjunction with hepatosplenomegaly, lipemia retinalis, premature atherosclerosis, and mild diabetes of the maturity onset type. Tolbutamide and standard glucose tolerance tests are abnormal. This picture may be seen in poorly controlled diabetes mellitus, glycogen storage disease, starvation, and stress states. Glucose utilization in adipose tissue may be decreased in these states, thereby providing less glycerol phosphate, and thus permitting fatty acid release from the fat cell. Again, reduction of carbohydrate intake seems to control the blood lipid concentrations.

Type V:

This is a mixed type characerized by an increase in chylomicrons, beta- and pre-betalipoproteins. Thus there are defects in the metabolism of both exogenous and endogenous lipid. There is usually a family history of diabetes and an early onset of atherosclerosis. This rare type is controlled by reduction of dietary fat *and* carbohydrate.

To recapitulate, concentrations of lipids and lipoproteins in the blood reflect the dynamics of lipid absorption, anabolism and catabolism. Thus, a defect in lipid metabolism may be demonstrated by elevation of one or more lipid components in the blood. Accurate diagnosis involves investigation of family history, of evidence for diabetes mellitus, as well as extensive studies on blood lipids; and of course, an accurate diagnosis is mandatory for adequate treatment and dietary control of these disorders.

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Konrad Bloch and Feodor Lynen

Nobel Prize for physiology and medicine—1964

K. BLOCH

F. LYNEN

Hypothesising upon the nature of a disorder involving a biosynthetic system before achieving a complete understanding of that system can be likened to the construction of the roof of a building before the supports are erected. It is to the foundation builders of cell chemistry that we must look to lend sufficient authority for the transformation of hypothesis into theory. Then a basis is established for the elucidation and ultimate correction of cellular metabolic disorders. For example, it is generally believed that a derangement of lipid metabolism associated with high serum cholesterol levels is a significant underlying factor in the pathogenesis of atherosclerosis. Only when the normal pathway of cholesterol formation was elucidated was definitive research possible into the mechanisms which control the levels of cholesterol in the blood and tissues.

For the revelation of most of the scheme of cholesterol and fatty acid synthesis, Professors Konrad Bloch of Harvard University and Feodor Lynen, director of the Max Planck Institute for Cell Chemistry in Munich, were awarded the 1964 Nobel Prize for physiology and medicine. Their research has been closely interwoven, but Bloch's main interest is cholesterol and Lynen's, fatty acids. The backgrounds of Bloch and Lynen are curiously related in respect to birthplace, early schooling, and the illustrious people who influenced their later life work.

Feodor Lynen was born in Munich, Germany in 1911 where his father was a prominent professor at the Technische Hochschule. He received his early training at the University of Munich working in the laboratory of Heinrich Wieland, a man who received the Nobel Prize in chemistry in 1928 with Windaus for work on the structure of cholesterol and related bile acids. Lynen's involvement in Wieland's investigations could not have been restricted to intellectual pursuits, for he allowed enough time to court and eventually marry Eva Wieland in 1937. In 1942 he accepted a lectureship at the University of Munich and was promoted to professor five years later.

Konrad Bloch was born in Neisse, Germany in 1912 and attended the Technische Hochschule from 1930 to 1934. During this period he developed a fascination for the work of the eminent chemists of that era.

> I soon became attracted to organic chemistry, especially the structure of natural products, an interest which I owed in large measure to the inspired teaching of Hans Fischer. Another influential experience was to attend the sessions

> of the Münchener Chemische Gesellschaft and to hear the great organic chemists of the time, Adolph Windaus, Heinrich Wieland, and Rudolf Willstaetter report their researches on steroids, porphyrins, and enzymes.[1]

After Hitler rose to power, Bloch fled Germany for religious reasons in 1934 to Davos, Switzerland where he obtained his first research post.

> My assignment here was to investigate the phospholipids of Tubercle bacilli, my first exposure to biochemical research.

After two years in Switzerland he decided to seek a new life and continue his education in the United States. In a short period, 1936 to 1938, Bloch resettled and earned a Ph.D. at Columbia University where he remained to do further research with Schoenheimer and Rittenberg.

> The few years spent at Columbia with Schoenheimer and his associate David Rittenberg were certainly the most influential of my "Lehrjahre". This period more than any other developed my lasting interest in intermediary metabolism and the problems of biosynthesis. During that time (in 1942) David Rittenberg and I initiated the work on the biological synthesis of cholesterol which was to occupy my research interests for nearly 20 years.[1]

In 1942 Bloch and Rittenberg used deuterium-labelled acetic acid to demonstrate this two-carbon compound to be a major precursor of cholesterol in rats. With this finding Bloch set as his future goal the complete elucidation of the pathway of sterol biosynthesis.

> The hydocarbon squalene proved a landmark in unravelling the biosynthetic pathway [of cholesterol]. Squalene is abundant in the livers of sharks and therefore Bloch planned to inject radioactive acetic acid into dogfish . . . isolate squalene from the livers, and test whether it is an intermediate in the overall synthesis of cholesterol.[2]

Although a seemingly tedious study, it led Bloch from the confines of his laboratory to the Bermuda beaches and shark hunting in 1947; however, the project proved a failure because the dogfish died in captivity. After a few days on the beaches Bloch returned to the laboratory where he demonstrated that squalene was indeed an important step in cholesterol synthesis using the more conventional rat as his experimental vehicle.

Although the early work of Bloch, Lynen, and many others revealed that cholesterol and fatty acids were formed from two-carbon fragments closely related to acetic acid, the chemical nature of these fragments remained a mystery. Lipmann initiated the solution to the problem with his discovery of coenzyme A. Subsequently, in 1951, Lynen isolated "active acetate" (acetyl-coenzyme A). In his Nobel lecture in 1964 Bloch credited his fellow researcher with supplying one of the most important keys in intermediary metabolism.

> Clearly, Lynen's fundamental discovery of acetyl CoA in 1951 paved a way for studying the early steps in sterol biosynthesis as it did for the understanding of all phases of fatty acid metabolism.[1]

The transformation of acetyl CoA to cholesterol involves about 36 steps and five main intermediate compounds which were worked out by Bloch and other experimenters over the years. "In 1958 Bloch and Lynen simultaneously identified the foundation stone of all terpenes occurring in nature, and therefore, . . . cholesterol."[3]

This compound, called isopentyl-pyrophosphate, filled one of the last remaining gaps in the biosynthetic pathway of cholesterol. The years of study eventually culminated in a workable scheme which allows investigation in different disciplines to achieve a better understanding of the abnormalities that may underlie many disease states.

> We can now predict that we, through further research in this field in the near future can expect to be able to do individual specific therapy against the diseases that in the developed countries are the most common cause of death.[1]

The motivating force which led to this contribution to our knowledge of cell biochemistry was expressed in Bloch's response to a toast during the Nobel ceremonies.

> I would not be here among you tonight but for the mentors, colleagues and students who have guided and aided me throughout my scientific life. . . . I have been happy to have chosen science as my career, and, to borrow a phrase of Jacques Barzun, have felt that "Science is, in the best and strictest sense, glorious entertainment."[1]

B. N. French, B.Sc. 6T8

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Special Review

Allergy To Stinging Insects

A. T. Lingys 6T7

Sting reactions from insects of the Hymenoptera order: bees, yellow jackets, hornets, and wasps may vary from mild local pruritus to anaphylactic death. The purpose of this article is to introduce the reader to this form of insect allergy, and to review the historical background, incidence, characteristics, etiology, diagnosis, and treatment of this condition.

HISTORICAL BACKGROUND

Only recent medical textbooks make reference to insect allergy, but the subject is not new. In 2641 B.C., King Menes of Egypt was stung to death by a wasp or hornet. Other reports of fatal sting reactions have been described sporadically in the medical literature,[1] and the cause of death was assumed to be toxic agents in the insect venom. 1914 Waterhouse[2] noted the similarity between severe insect sting reactions and anaphylactic shock in experimental animals, and suggested an allergic mechanism. The growth of immunology expanded the interest in insect allergy, and in 1925 desensitization with bee extract[3] was attempted for the first time. In 1930 Benson and Semenov[4] wrote a classic paper confirming the allergic nature of systemic sting reactions. Research in this field is continuing, with special emphasis on the immunological aspects of insect allergy.

INCIDENCE

Insect allergy has been observed in all parts of the world, and in Canada it is estimated[5] that at least one thousand people have moderate to severe allergy to Hymenoptera stings. Parrish[6] reports that about thirty persons are killed each year by insect stings in the United States. His statistics show that more deaths are due to bee stings than to rattlesnake bites per year. In addition, sudden deaths of unknown cause may be due to insect sting reactions.

CHARACTERISTICS OF ALLERGY TO STINGING INSECTS

Many investigators have collected data on individuals with unusual reactions to insect stings. A study of three hundred such people in Ontario has been made by R. Bladek.[5 15] He has found that most of the victims have a history of previous exposure to Hymenoptera insects, and of increasing severity of symptoms with each subsequent sting. In this study the manifestations of sting reactions in order of frequency were: generalized urticaria, malaise, generalized edema, wheezing, dyspnea, abdominal pain, nausea and vomiting, and drowsiness. Shock symptoms were experienced by fifty percent and coma by thirteen percent of the patients. Skin disorders of allergic etiology, viz. urticaria and infantile eczema were commonly found in these individuals, and their family history was often positive for atopic disease (eczema, hayfever, and asthma). Skin tests with extracts of the suspected insect did not give good correlation with the severity of the sting reaction. These findings are supported by Mueller,[7] Schwartz,[8] Trinca,[9] and the Insect Allergy Committee of the American Academy of Allergy.[10]

ETIOLOGY OF STING REACTIONS

1) Toxicity

The female Hymenoptera is equipped with a stinging mechanism consisting of an acid and an alkaline gland leading to a poison sac, and a modified ovipositor serving as the stinger. A minute amount of venom is injected intradermally. Chemical analysis of the venom has revealed the following constituents: histamine, serotonin, and bradykinin (all are smooth muscle stimulants); lecithinase, hyaluronidase (which assists the permeation of venom), and a saponin-like substance comparable to that found in snake poisons. These agents give rise to the local pain and wheal of any insect sting, but they are not responsible for severe local or systemic reactions suffered by one sting. However, fatalities from many hundreds of stings are known, and in these cases the toxicity of the large volume of venom injected is implicated. But the toxic mechanism cannot explain anaphylactic death from a single sting, nor the increasing severity of reactions with repeated stings in certain people.

2) Allergy

More than thirty years ago, Benson and Semenov[4] demonstrated that insect sting reactions were due to a water soluble protein fraction derived from the insect's body and included in the poison, and not to the pharmacologic agents in the venom. Other workers[12] using the Ouchterlony gel diffusion method showed that extracts of bee, yellow jacket, and wasp contained four to six antigenic fractions. The injected insect body protein is a foreign substance which stimulates the production of specific antibodies. After an interval of time, a second injection of the same venom presumably results in the union of the antigens and the antibodies thus rendering the antigen inactive. In this way repeated stings by the same insect should result in diminished responses, and this is called immunity. On the other hand repeated stings may result in an increased response, and this is known as allergy. The reason why certain individuals react abnormally, i.e. are allergic to insect stings is not fully understood, but most likely an altered immune mechanism is at fault.

Immunologic evidence necessary to support an allergic etiology of systemic sting reactions must include:

1) the identification of the offending antigen(s), 2) the demonstration of antibodies in susceptible individuals, and (3) the demonstration that the antigen-antibody union is the actual cause of the clinical symptoms. The antigens are insect body proteins as describe above. Studies[13 14] for specific antibodies in the sera of patients sensitive to stinging insects have yielded inconclusive results. The clinical symptoms of systemic sting reactions resemble those of anaphylaxis and both conditions may involve the skin, respiratory tract, gastrointestinal tract, and cardiovascular system. The pathogenesis of the symptoms is the stimulation of smooth muscles and blood vessels by highly active pharmacologic substances (histamine, serotonin, plasma kinins, and slow-reacting substance [a prostaglandin]) which are released from damaged tissue cells as a consequence of antigen-antibody union.

DIAGNOSIS

A detailed, accurate clinical history is the most reliable means of diagnosis. Emphasis should be placed on the signs and symptoms, previous stings and their symptomatology, noting especially the tendency to increasingly severe reactions, the identification of the insect if possible, and personal and family history of allergic disorders.

Skin tests with insect extracts are of doubtful diagnostic significance, since about forty percent of the "normal" population give positive results. Nevertheless skin tests are useful to confirm the diagnosis, to demonstrate cross-sensitivity to the various species of Hymenoptera, and to determine the starting dose of extract for desensitization.

TREATMENT

1) Emergency treatment of a severe systemic reaction

The treatment of a severe sting reaction i.e. acute anaphylactic shock, is directed toward the reduction of the rate of antigen absorption, and the maintenance of a patent airway and a normal blood pressure level. If the sting is on an extremity, a tourniquet should be applied proximal to the sting site to slow down venom absorption. In the case of a honey bee sting, the remaining stinger in the skin should be removed by scraping it sideways. Adrenaline is the drug of choice to relieve bonchospasm and laryngospasm, and it should be given immediately in a dose of .5cc. of 1/1000 solution subcutaneously. This dose should be repeated in twenty minutes if necessary. If adrenaline is not available, a sublingual tablet of isoproterenol can be substituted. The patient should be taken to the nearest hospital for further observation, and any subsequent treatment will depend on the clinical condition. Antihistamines and steroids are probably useless in an emergency situation. Individuals who are aware of their allergy to insect stings should carry an emergency kit equipped with adrenaline and isoproterenol tablets on their person at all times.

2) Desensitization

Every person who has experienced a systemic reaction to an Hymenoptera sting has a sixty five percent chance of suffering progressively more severe reactions.[11] Workers[7 15] in this subject have found desensitization with insect extracts to be ninety percent effective, and they highly recommend desensitization as a means of prophylaxis. The duration of desensitization has not been firmly established, but it should be continued for at least two or three years.

SUMMARY

Some people suffer a systemic reaction from a single sting of an insect of the Hymenoperta order. The cause of this reaction is allergy to insect body protein which is incorporated in the venom. Because skin tests are equivocal and serological tests are still in a developmental stage, the diagnosis of insect allergy is best made from a clinical history. In an emergency situation the first drug of choice is adrenaline and secondly a sublingual isoproterenol tablet. Any person with a history of a systemic insect sting reaction should benefit from a course of desensitization and insect extracts.

ACKNOWLEDGMENTS

I wish to thank Dr. R. Bladek of the Toronto Western Hospital for his guidance, encouragement, and enthusiasm during the study of this project.

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Clinicopathological Conference

Hepatosplenomegaly and Progressive Neurological Deterioration In A Three Year Old Female Child

W. Laird 6T8

CASE PRESENTATION

A three year old child was admitted to the hospital three months prior to death because of rapidly progressive mental deterioration and severe motor disturbances.

The child was the full term product of a normal pregnancy and delivery but after several months the parents noticed that her development was somewhat retarded. Her appetite was fair but there was often dysphagia and the child remained small and gained weight poorly. She was unable to sit up without support until fourteen months of age and had never walked. Even at two years of age she had required support in standing. By this age the child could refer to her parents by name and respond to simple commands.

Thirteen months before death the patient suddenly developed a febrile illness with a temperature of 107° F. and delirium. Penicillin therapy was successful and no complications ensued. However, one month after this illness the parents noticed that the child began to regress physically and mentally. Over the next nine months she lost the ability to stand or sit and developed gradually increasing spasticity of the extremities. She was unable to speak and suffered complete loss of comprehension. Moreover, by the time of hospitalization the mother felt that she was blind. There were no convulsions at any time.

The history of past health revealed an episode of epistaxis and umbilical bleeding at thirteen days of age. Then on the fifteenth day she had rapidly become jaundiced and hepatosplenomegaly was discovered at this time. The jaundice disappeared at about six months of age but the hepatosplenomegaly persisted, evidently without further enlargement. The only other abnormalities on functional inquiry were a persistent cough of undetermined duration, intermittent constipation, and difficulty in sleeping.

Inquiry into the family health revealed that an older brother also had jaundice and hepatosplenomegaly at birth and had died at eight months. At autopsy, cirrhosis of the liver was diagnosed. Another older brother was alive and well. It was interesting that at the time of the patient's hospitalization a younger sister was herself being investigated for hepatosplenomegaly and jaundice beginning on the tenth postpartum day. The maternal grandmother had died from "cancer of the spleen" and the paternal grandmother was a mild diabetic. The patient's father had two siblings: a sister who was retarded and a brother who died at two months of age. Both parents were alive and well and the family history was otherwise noncontributory.

Physical examination revealed a pale, emaciated child lying listlessly and seemingly unaware of her surroundings. The head and neck were unremarkable and the chest was clear. The heart sounds were normal but there was a soft grade I/VI systolic murmur heard over the precordium. The abdomen was distended but neither a fluid wave nor shifting dullness was demonstrable. The liver was palpable, the border being felt 5 cm. below the right costal margin in the anterior axillary plane. It was firm and smooth. The spleen also was felt 8 cm. below the left costal margin in the anterior axillary plane. It was freely moveable but very firm. On neurological examination marked abnormalities were evident. The child was unable to speak and showed no comprehension; there was virtually no voluntary motor activity and the extremities showed marked spasticity. The deep tendon reflexes were hyperactive 4^+ bilaterally. There were no abnormalities on fundoscopic examination but further examination revealed loss of light fixation and the child was believed to be blind.

Urinalysis was negative for sugar, protein, ketones and bilirubin but 1^+ for urobilin. On microscopic examination of the urine some epithelial cells and the occasional white blood cell were seen. Liver function tests were unremarkable—the BSP retention was 36% after five minutes, 3% after fifteen minutes, and O after forty-five minutes; the prothrombin time was 18 secs. (control 15 secs.). The parents were both Wassermann negative. Radiological examination of the skull was normal. The chest X-Ray showed an accentuated bronchovascular pattern and a patchy peribronchial infiltration of the lower right lung suggestive of a respiratory infection with only slight parenchymal involvement. The long bones were osteoporotic with epiphyseal development in the extreme low normal range. There was marked ulnar deviation of the wrists and along with the generalized soft tissue wasting the picture was not unlike

the muscular dystophies. The patient's blood type was Group O, RH^+. The hemoglobin was 7.0 gm. The smear revealed large vacuolated white cells and some mononuclears were fenestrated. A bone marrow aspiration biopsy was taken and revealed almost complete aplasia of the normal myeloid tissue. In addition, numerous large reticuloendothelial cells with pale, vacuolated cytoplasm were seen.

The patient was discharged. After further deterioration of her condition, she died at home three months later at the age of three and a half years.

The case history above was presented to Dr. J. A. Lowden of the Hospital for Sick Children and his discussion of the differential diagnosis follows:

DR. J. A. LOWDEN: The case history and physical findings outlined above present a problem in the differential diagnosis of progressive neurological deterioration associated with hepatosplenomegaly and neonatal jaundice. In a child of this age, this combination of signs is unlikely the result of an acquired disease since infections, tumours, etc. rarely involve the two organ systems in such a progressive fashion and yet allow the child to survive so long. Two congenital infections are possible. *Toxoplasmosis* presents in this fashion but with pronounced neurological signs from birth. It can be readily ruled out by examination of the urine and skull films. *Congenital syphilis,* another unlikely diagnosis I feel, could be considered and a blood Wassermann on both parents was done with a negative result.

The reticuloendotheliosis group, collectively labelled Histiocytosis-X might possibly involve both systems. *Letterer-Siwe diseases* is the most likely, but the absence of skin lesions and the marked neurological changes would rule against this diagnosis. One could, however, look for radiological evidence of bony lesions and examine the marrow.

In younger infants one might consider *galactosemia* but this child had a reasonably normal neonatal period, except for mild jaundice. Galactosemia results in severe early jaundice and is usually fatal in the first few weeks if undiagnosed. Similarly erythro-blastosis foetalis and glucose-6-phosphate dehyydrogenase deficiency will both produce severe anemia and jaundice in the new-born. They may result in kernicterus and hepatosplenomegaly but such children show very early neurological signs and, if they survive the condition is not progressive.

Wilson's disease · (hepatolenticular degeneration) should be considered but in children cirrhosis and signs of liver failure usually develop long before neurological signs become evident. Although occasional tremor and myoclonus are described, mental retardation is not common. I think this diagnosis is unlikely but copper levels in the blood and urine and a serum ceruloplasmin estimation would be useful.

Gargoylism in one of its variants may present as did the patient but progressive skeletal changes usually follow and the patients develop a classical facies, spade-shaped hands and spinal abnormalities. X-Rays of the long bones and increased amounts of acid mucopolysaccharides in the urine are diagnostic.

I feel that the combination of signs and the clinical course of the child's disease are most strongly suggestive of an inborn error or metabolism, likely a lipid-storage disease. There are two conditions which classically follow the pattern described — *Niemann-Pick disease* and infantile *Gaucher's disease*. In both cases an abnormality in the metabolism of sphingolipids results in the accumulation of lipid in liver, spleen, and other reticuloendothelial organs. In Niemann-Pick disease, however, there is more widespread involvement and lipid also accumulates in lung, thyroid, adrenals and a host of other organs. The lipid (cerebroside in Gaucher's disease and sphingomyelin in Niemann-Pick disease) collects in large pale foamy cells with irregular nuclei. The cells are very similar in the two conditions and few pathologists can differentiate them. The importance of a well-documented family history can be seen at this point since both diseases are hereditary and the story of similar disease in two of the child's siblings is one of the strongest reasons for thinking along these lines.

However, I would lean towards a diagnosis of Niemann-Pick disease for several reasons. Although in both diseases abnormalities of cerebral lipids can produce the neurological signs seen in the patient, her chronic cough suggests a pulmonary infiltration and therefore, Niemann-Pick disease. Her neonatal jaundice also points in this direction. Moreover, patients with Gaucher's disease tend to present with a massive splenomegaly with only moderate hepatomegaly. Lastly, on a statistical basis, infantile Gaucher's disease is very rare and many believe it is not a real disease but is mis-diagnosed Niemann-Pick disease.

Diagnostically, one may find foam cells in biopsies of lymph nodes, liver, or marrow. Also, a rectal biopsy showing lipid storage in the cells of the myenteric plexus suggests a sphingolipidosis. Foam cells in sputum samples, a radiological appearance of bronchopneumonia in an afebrile child and lack of bony lesions on X-Rays of the long bones are more specific for Niemann-Pick disease. Despite these methods the diagnosis usually depends on the demonstration of increased amounts of the appropriate lipid in biopsy tissue or autopsy material. The lipids are distinguished readily by thin layer chromatography.

POST MORTEM FINDINGS

The body was emaciated and had virtually no subcutaneous fat. The skin was pale and yellowish-brown. The body was in a position of decerebrate rigidity with the wrists and fingers flexed, the legs abducted and ex-

FIG. 1. This picture shows clearly the marked generalized spasticity and extreme wasting.

tended at the hips, the knees everted, and the feet in equinovarus positions.

The liver extended 5 cm. below the right costal margin in the anterior axillary plane and weighed 468 gm. (normal 418 gm.). Grossly it was very firm, pale and covered with red streaks. The surface suggested a fine parenchymal scarring and on microscopic examination a diffuse but mild cirrhosis was evident. The sinusoids contained foamy reticuloendothelial cells, though this was not prominent.

The spleen extended 7 cm. below the left costal margin in the anterior axillary plane and was markedly enlarged on gross examination. It weighed 138 gm. (normal 37 gm.) and was pale and firm. The cut surface was orange, finely granular, and the Malpighian

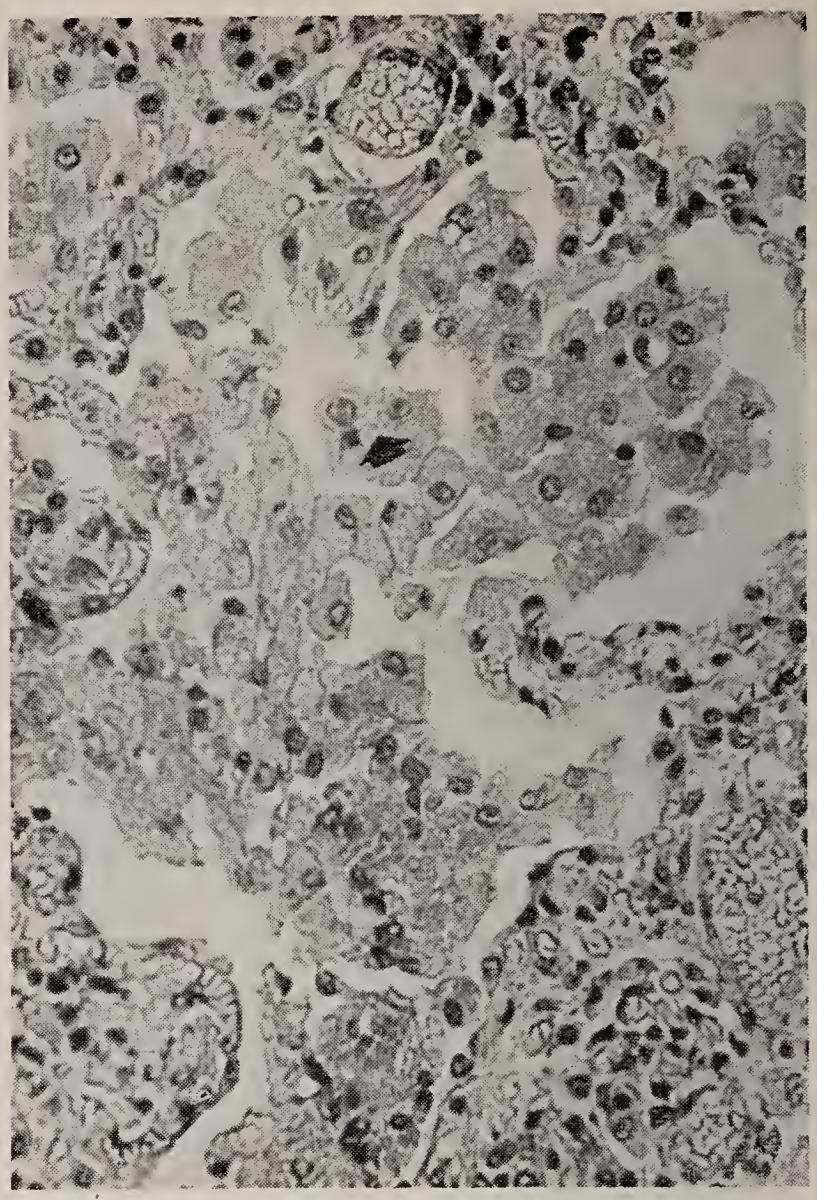


FIG. 2. Photomicrograph x 1000 Lung. Niemann-Pick Cells are seen in an alveolus (A). The typical foamy cytoplasm is evident.

bodies could not be identified. The microscopic appearance was abnormal, revealing a diffuse infiltration of innumerable foam cells similar to those in the hepatic sinusoids.

Marrow specimens from the ribs, vertebral bodies and upper femur were extremely pale and on microscopic examination revealed the same picture as the antemortem aspiration biopsy.

Generalized lymphadenopathy was evident and the nodes were an abnormal bluish colour. The normal follicular pattern was destroyed and the sinusoids (including those of the tonsil) were filled with many foam cells. Innumerable large foam cells were seen throughout the thymus.

On gross examination the lungs were enlarged, firm and had the appearance of massive consolidation. Both weighed 50% more than normal. The cut surface was haemmorhagic, and greasy, and a milky fluid was expressed. Microscopically, the lungs were filled with the typical foam cells seen in other organs. Much of the normal structure was disrupted, and the normal re-

maining lung tissue revealed a widespread confluent pneumonia.

The mucosa of the trachea and main bronchi was fiery red and on microscopic examination revealed an infiltration of polymorphonuclear cells.

On gross examination the brain was small, firm and appeared atrophic. The anatomical pattern was intact but the sulci were widened and the gyri wasted. Microscopically, the brain showed severe degenerative changes similar to Tay-Sach's disease. The neurons were felt to be reduced in number and degenerative. Some were enlarged and vacuolated like fatty cysts. The myelin also was degenerated. There was a generalized cerebral gliosis and many lipid-filled lipophages were seen.

In the pylorus the neurons of the myenteric plexus were swollen but did not contain lipid. Similar neurons were seen throughout the myenteric plexus of the gut and also in the ganglion cells of the adrenal gland.

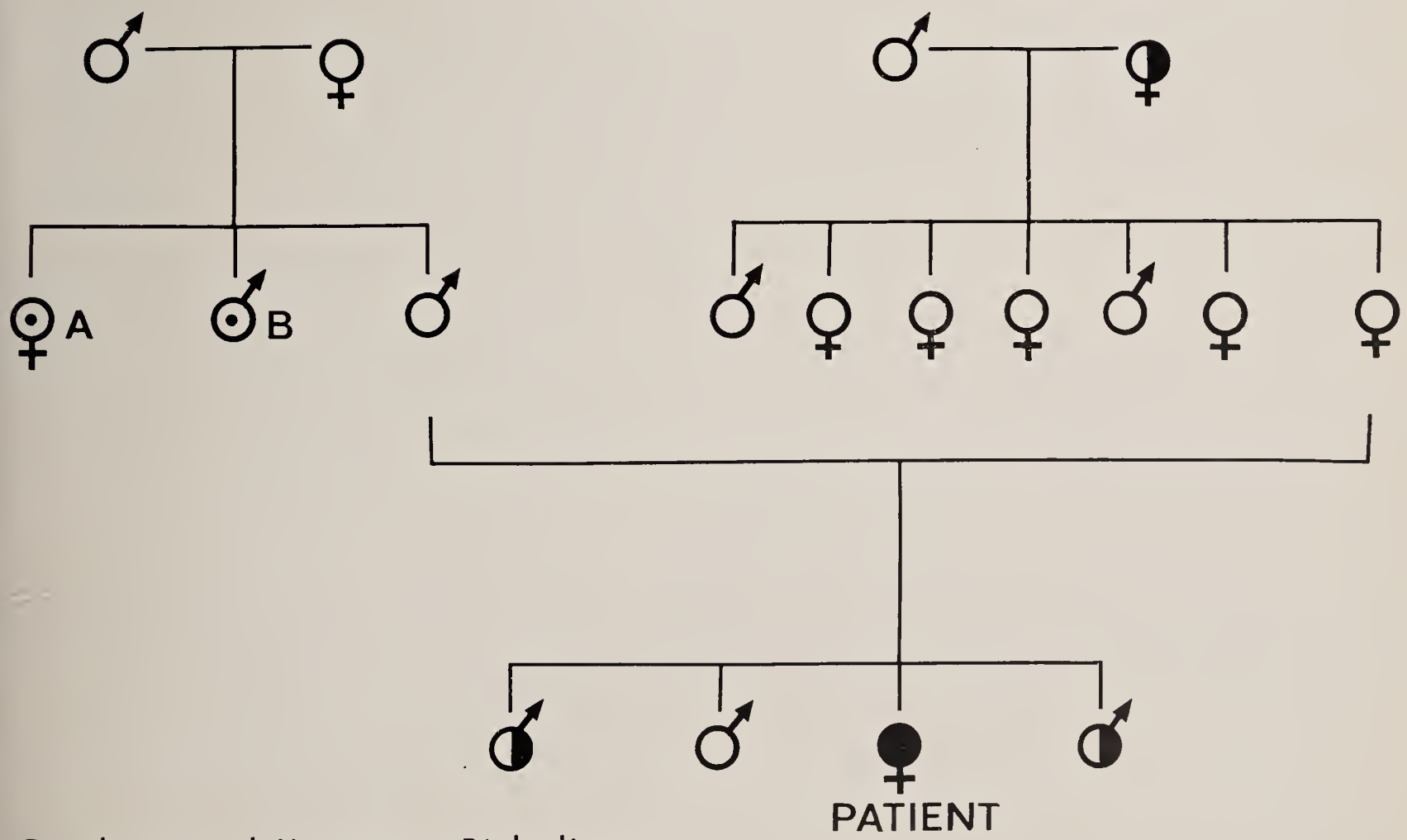
Lipid analysis was undertaken using special fat stains and chemical analysis. The foam cells were found to stain quite uniformly. In paraffin sections the intracellular lipid did not dissolve with the alcohol fixative as do most lipids. Some of the foam cells stained strongly PAS positive while others were only faintly PAS positive.

Chemical analysis done on splenic and hepatic tissue revealed in both a moderately elevated phospholipid content, a greatly elevated sphingomyelin content and a slight increase in cerebroside content.

The marked elevation in the sphingomyelin content confirmed the clinical diagnosis, and an anatomical diagnosis of Niemann-Pick disease complicated by bronchopneumonia was made.

An interesting feature of the case came to light later. Because of the hereditary nature of Niemann-Pick disease (it is believed to be inherited as a simple Mendelian recessive), it was decided to re-examine the autopsy material from the patient's elder brother and maternal grandmother. The sections from the latter case were obtained from the hospital where she had ostensibly died from cancer of the spleen. On examination there were found to be typical Niemann-Pick cells in the spleen. The sections from the patient's brother, diagnosed at autopsy as cirrhosis of the liver, also revealed Niemann-Pick cells in many tissues. A family pedigree was then constructed (Fig. 3).

FIG. 3.



FURTHER DISCUSSION

A positive diagnosis of Niemann-Pick disease cannot be made without lipid analysis of the involved tissue. Nevertheless, it seems clear that the elder brother and younger sister of the patient were afflicted also with the disease. The case of the maternal grandmother is also interesting as to the best of our knowledge there have been only two previous cases of an adult form of Niemann-Pick disease described in the literature.[1 2]

Crocker has suggested the division of Niemann-Pick disease into four clinical types.[3]

1. Type 1 (classical Niemann-Pick disease). These patients, usually of Jewish extraction, tend to have marked hepatosplenomegaly and commonly have respiratory involvement clearly visible on X-ray. They develop neurological symptoms early in infancy. The lipid content in the blood and tissues is elevated. Neonatal jaundice is a very variable finding. Death usually occurs at one to two years of age.

2. Type 2 (non-cerebral Niemann-Pick disease). These patients also have hepatosplenomegaly and radiological evidence of pulmonary infiltration. However, they have no neurological symptoms, tend to always have neonatal jaundice and the racial background is mixed showing no Jewish predisposition. Death usually occurs by the age of one year.

3. Type 3 (moderate course Niemann-Pick disease). In this type hepatosplenomegaly is less marked, there are no chest symptoms and neurological symptoms occur in late infancy. The blood lipids are not elevated and tissue lipids tend to be less elevated than in types 1 and 2. Death usually occurs at the age of three to five years.

4. Type 4 (Nova Scotian group). These patients tend to have very variable signs and symptoms and will not be discussed here.

The patient in the case described clearly does not belong completely to any one type but rather had a combination of the signs and symptoms of types 1 and 2. However, this is not difficult to understand for, as will be explained below, if there is considerable overlap of the lipids involved in different lipid-storage diseases it stands to reason that the genetic coding responsible for Niemann-Pick disease could also be very variable. In fact, it might be postulated that a very mild form of the disease *is* possible which would allow the patient to reach adulthood as did the maternal grandmother.

Storage diseases, as the name implies, are inherited inborn errors of metabolism, characterized by the excessive accumulation of a substance which may or may not be a normal endogenous product of body metabolism. Or, as in the case of galactosemia, the substance which accumulates may be derived from an exogenous source. The therapeutic implications of this are obvious: galactosemia can be controlled by withholding galactose from the diet, whereas in the sphingolipidoses, where an endogenous metabolite is stored, there is no therapy available at the present time. An attempt will not be made here to discuss all the lipidoses in detail but merely to present a frame of reference with which to consider these diseases.

The sphingolipidoses comprise a group of storage diseases in which sphingolipids are stored in excessive amounts in various tissues of the body. Included in this group are: Gaucher's disease, Niemann-Pick disease, Amaurotic Family Idiocy (the infantile form of which is Tay-Sachs disease) Metachromatic Leukodystrophy, Generalized Gangliosidosis, and Fabry's disease. The clinicopathological features of the particular disease depend on which lipid is stored in which tissues and thus, which organ system (or systems) is functionally disrupted. In many cases the clinical pictures are strikingly similar, as in infantile Gaucher's disease and Niemann-Pick disease, and a lipid analysis therefore is always indicated.

The basic lesion in storage diseases is an inherited enzymatic defect. This defect can result in excessive storage in two ways. Firstly, there may be abnormalities in anabolic pathways concerned with the formation of a substance, and in these cases a precursor accumulates; secondly, there may be abnormalities in catabolic pathways which a given substance cannot be broken down. Thus, in Tay-Sachs disease an abnormality in the anabolic enzymatic pathway prevents the addition of galactose to a precursor of the normal ganglioside. In Gaucher's or Niemann-Pick disease, on the other hand, an abnormality in an enzyme system required for the catabolism of a normal sphingolipid results in the accumulation of an insoluble material which cannot be removed. The specific enzymes involved in Gaucher's disease, Niemann-Pick disease, and Metachromatic Leukodystrophy have recently been identified[4] and further work will no doubt uncover the defects in the remaining sphingolipidoses.

In recent years the trend has been to consider the various sphingolipidoses as part of one "disease complex". This has come about for several reasons. First, it has been known for some time that the particular lipids which accumulate in these diseases have a common structural unit known as CERAMIDE. This is a substance composed of the amino alcohol sphingosine linked to a fatty acid. This idea of a common structural unit has perhaps been overemphasized because the fatty acid portion in the various diseases is different and the pathways for the synthesis of ceramide are also probably different. Another reason for this "disease complex" concept is the fact that as more work has been done it has become increasingly obvious that at least some of the diseases involve multiple defects. As

a result although each disease has one lipid characteristically much elevated, other lipids are also elevated and there is indeed some degree of overlap among the various lipidoses. For example, gangliosides, the accumulation of which is characteristic of Tay-Sachs disease and Generalized Gangliosidosis, have been shown to accumulate in Niemann-Pick disease as well. Moreover, the accumulation of gangliosides (and not sphingomyelin) in Niemann-Pick disease may, in fact, be often responsible for the neurological damage seen. In conclusion it is clear that the biochemical mechanisms responsible for the lipid storage diseases require further elucidation which, it is hoped, will improve the present gloomy prognosis of these diseases.

ACKNOWLEDGEMENT

The help of the photography department, Hospital for Sick Children is gratefully acknowledged.

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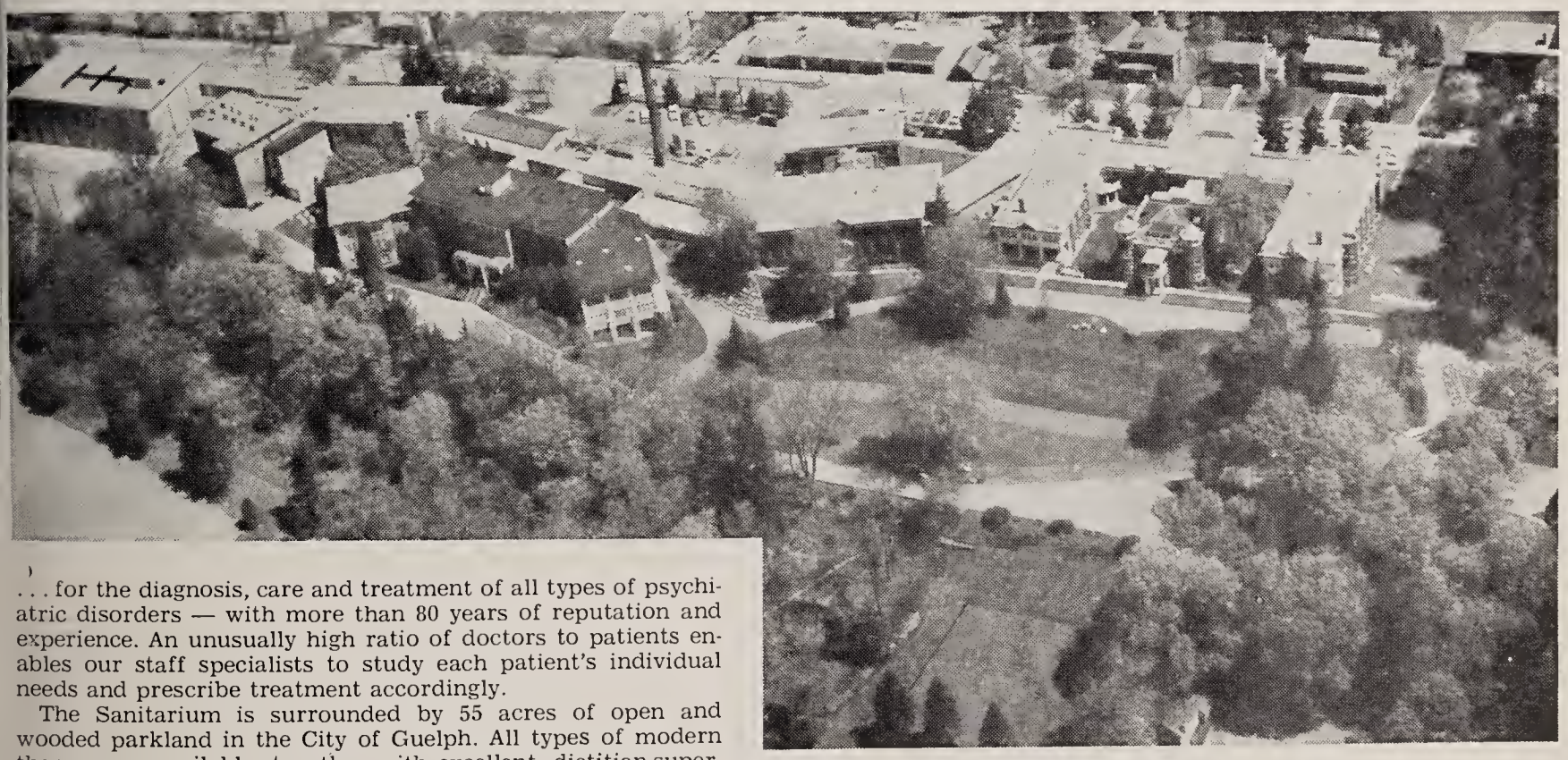

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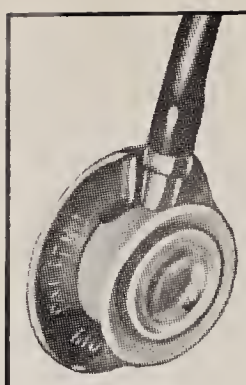

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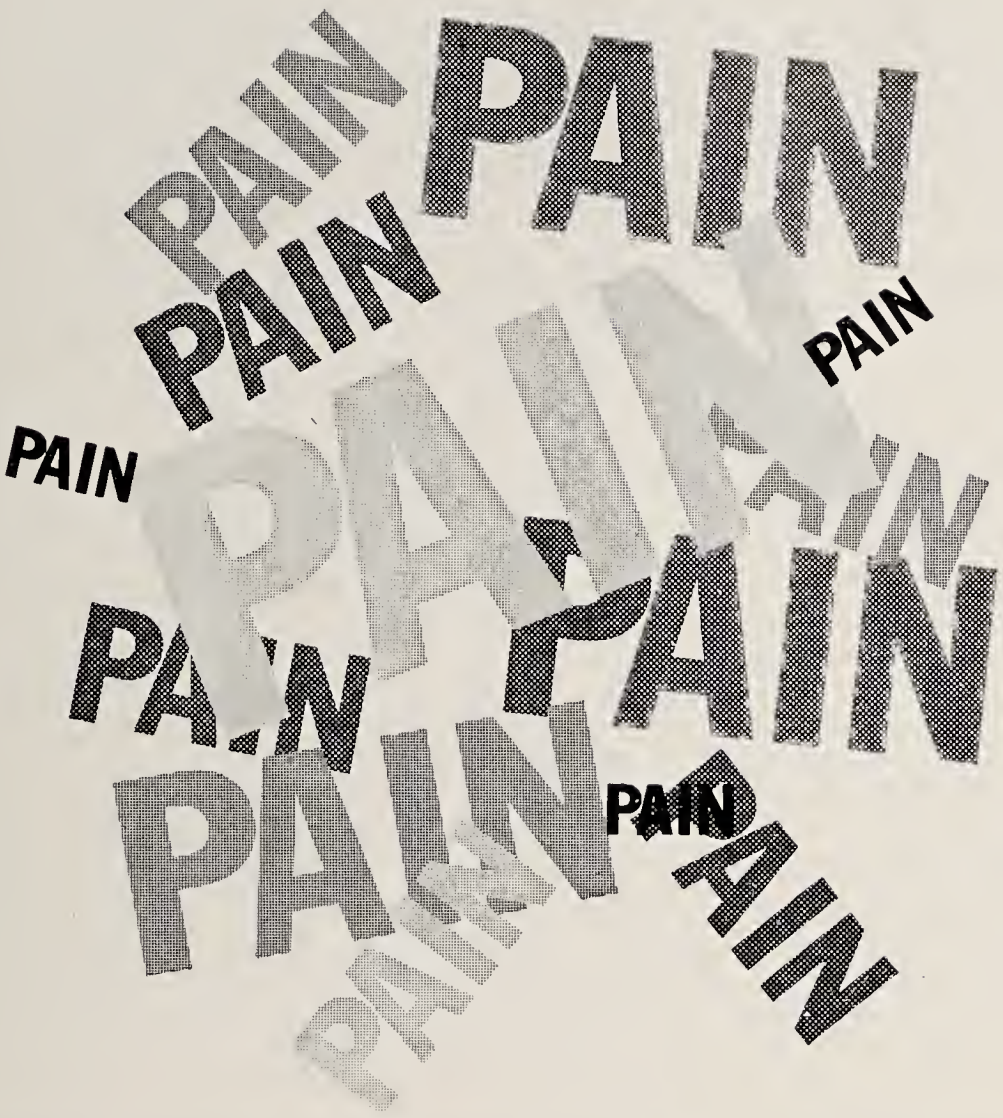

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